PB90-186438

Neurotoxic Effects of Controlled Exposure to a Complex Mixture of Volatile Organic Compounds

(U.S.) Health Effects Research Lab., Research Triangle Park, NC

Mar 90

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1. REPORT NO. HERL-0727 EPA/600/1-90/001	2.	3. RECIPIENT'S ACCESSION NO.
4. TITLE AND SUBTITLE Neurotoxic effects of controlled exposure to a complex mixture of volatile organic compounds		5. REPORT DATE 7/39 6. PERFORMING ORGANIZATION CODE HERL/HSD/CPB
7. AUTHOR(S) D. Otto,[1] L. Molhave,[2] G. Goldstein,[1] J. O'Neil,[1] D. House,[5] G. Rose,[3] J. Berntsen, W. Counts,[3] S. Fowler[1], K. Hudnell[4]		8. PERFORMING ORGANIZATION REPORT NO. HERL-0727
9. PERFORMING ORGANIZATION NAME AND ADDRESS 1. HERL/HSD 2. Inst. Env. Occup. Med., Univ. Au hus, Denmark 3. RSI Environ., RTP, NC 4. HERL/NTD 5. HERL/RRSD		10. PROGRAM ELEMENT NO. 11. CONTRACT/GRANT NO. N/A
12. SPONSORING AGENCY NAME AND ADDRESS		13. TYPE OF REPORT AND PERIOD COVERED Project Report 14. SPONSORING AGENCY CODE EPA/600/10

15. SUPPLEMENTARY NOTES

For distribution to interested scientists and public

16. ABSTRACT

Subjective reactions of discomfort, impaired air quality, irritation of mucosal membranes, and impaired memory have been reported in chemically sensitive subjects during exposure to volatile organic compounds (VOC's) found in new buildings. 66 normal healthy male subjects aged 18-39 were exposed for 2.75 hrs to a complex VOC mixture at 0 and 25 mg/m^3. Each subject completed control and exposure sessions at one week intervals in counterbalanced order. Measurements included comfort ratings of eye, nose and throat irritation, symptom questionnaire and computerized behavioral tests. Subjects found the odor of VOCs unpleasant strong and reported that VOC exposure degraded air quality, increased headache and produced general discomfort. VOC exposure did not affect performance on any behavioral tests. Results indicate that subjective reactions to VOCs are not limited to chemically sensitive individuals since the study population is a subgroup that is probably least likely to be affected by chemical exposure.

KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

17. DISTRIBUTION STATEMENT Release to public	19. SECURITY CLASS (This Report) UNCLAS 20. SECURITY CLASS (This page) UNCLAS	21. NO. OF PAGES 105 22. PRICE A06

PB90-186438

EPA/600/1-90/001
March 1990

FINAL REPORT (Deliverable 2520)

NEUROTOXIC EFFECTS OF CONTROLLED EXPOSURE TO A COMPLEX MIXTURE OF VOLATILE ORGANIC COMPOUNDS

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Sources of Support: EPA Contract 68-02-4179 (Combustion Engineering)
EPA Contract 68-02-3800 (Subject Recruitment)

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U.S. DEPARTMENT OF COMMERCE
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A. EXECUTIVE SUMMARY

Growing public awareness of the potential health hazards of chemicals found in the indoor environment has given rise to the definition of a new problem designated as sick (or tight) building syndrome (SBS). SBS is characterized by irritation of the eyes, nose and throat. Preliminary evidence from Danish studies (Molhave et al, 1986; Kjaergaard et al, 1989) also indicates effects on cognitive functions such as memory. Many of the chemicals found indoors that have been linked with SBS are volatile organic compounds (VOCs). Congress has mandated EPA to characterize the sources, real-world exposure levels and health risks of indoor pollutants. Little information is currently available on the health effects of exposure to VOC mixtures found in new or renovated buildings. EPA has established an intramural research program to address this question. The current report details the results of the initial study in this program.

Objectives of this study were to confirm and extend the pioneering work of Molhave et al (1986) and to identify sensitive measures for use in subsequent studies of sick-building syndrome. Molhave et al. demonstrated sensory irritant and neurobehavioral effects of controlled human exposure to a complex VOC mixture at concentrations of 5 and 25 mg/m3, representing the usual and maximal levels found in new homes. The design of the Danish experiment was problematic, however. A repeated-measures design was used in which subjects completed clean air and exposure conditions in the morning and afternoon of the same day. Three types of confounding may have occurred in this design--practice effects, VOC exposure carry-over effects from morning to afternoon, and time-of-day differences. The present study was designed to minimize or eliminate these problems by scheduling a separate training day to minimize practice effects, testing all subjects at the same time of day (afternoon), and separating clean air and exposure runs by a minimum interval of one week.

Other important differences between studies included the subject population

and tests used. The Danish study included both males and females aged 18-64, all with documented histories of chemical sensitivity. The present study was limited to young adult males aged 18-39 with no history of chemical sensitivity. Only two neurobehavioral performance tests were used in the Danish study, while fourteen tests were used in the present study to fully characterize the nature of the possible neurobehavioral effects of VOC exposure.

Results of this study confirm the adverse subjective reactions of subjects to a 25 mg/m3 concentration of volatile organic compounds reported by Molhave et al. Ratings of general discomfort (defined as irritation of the eyes, nose and throat), symptom questionnaire responses on odor intensity, air quality, eye and throat irritation, headache and drowsiness, and mood scale measures of fatigue and confusion all differed in predicted directions between clean air and exposure conditions. However, no convincing evidence was found of any neurobehavioral impairment associated with exposure to the VOC mixture. That is, we were unable to confirm the Molhave et al report that VOCs impair short term memory as measured by auditory digit span. Nor were other tests of memory, sensorimotor performance, or more complex cognitive functions affected by exposure to this concentration of VOCs. In summary, clear adverse subjective reactions to VOC exposure, but no functional (neurobehavioral) impairments, were found.

Confirmation of sensory irritation in a normal, healthy adult male population is quite important. This finding demonstrates that subjective reactions to VOCs at levels found in new buildings are not limited to "complainers" or chemically sensitive subgroups in the general population. In fact, subjects in this study probably represent the subgroup least likely to be affected by VOC exposure. Sensory irritation, headache and drowsiness are also of considerable importance in the community and workplace. Perceived dissatisfaction with air quality in the home, office, market place, or factory can lead to reduced productivity, decreased quality of life among home-owners and workers, and could result in mass exodus from buildings with air quality problems. This is an important factor in the sick-building syndrome. Further consideration should be given to the relevance of subjective reactions in

evaluating the adverse health effects of indoor pollutants.

Subjects in this study and previous Danish studies found the odor of VOCs to be very strong and unpleasant. The unmistakable odor of VOCs confounds efforts to conduct a double-blind experiment. Subjective reactions to the VOC mixture can be attributed, at least in part, to the unpleasant odor. If this were the only objectionable characteristic of VOCs, we would probably conclude that VOCs at concentrations found in the indoor environment do not constitute any significant health risk. The time course of responses to odor and symptoms of irritation differ, however, suggesting that odor accounts for only part of the subjective reaction to VOCs. Further study is needed to differentiate olfactory and trigeminal components of the VOC response.

Failure to find any functional consequences of exposure to the VOC mixture however, raises important questions in assessing health risks and planning subsequent indoor air studies. For instance, we cannot conclude that a 25 mg/m3 concentration of VOCs poses no neurotoxic risk to susceptible subgroups of the general population, or even to the general population. Further study with a chemically sensitive group of subjects is needed and the relationship of age and gender to VOC response needs to be explored. It is also possible that the neurobehavioral tests used were not sensitive (or difficult) enough to detect effects. If subjects find that VOCs irritate the eyes and throat and induce headaches, one would expect performance to be impaired, at least indirectly, by distraction or impaired attention.

Another possibility to consider is physiological endpoints. If VOCs irritate the eyes, nose and throat, we should examine secretions of these tissues for evidence of inflammation. Kjaergaard et al (1989) recently reported evidence of inflammatory response in eye fluids following VOC exposure. However, no evidence of inflammatory response in nasal secretions was found, consistent with symptom response in the present study. Further study of inflammatory effects of VOC exposure in eye fluid and other mucosal tissues are needed.

B. BACKGROUND AND RATIONALE.

"Sick Building Syndrome" costs industry and the government considerable time and dollars in lost worktime, worker dissatisfaction, and temporary abandonment of facilities (Melius et al, 1984). Beyond the economic impact is the question of possible adverse health effects of exposure to indoor air pollutants found in new and renovated homes and commercial buildings. Most people spend the majority of their lives indoors (NRC, 1981). Therefore, agencies and institutions responsible for protecting human health therefore need to carefully study the potential adverse effects of chemicals commonly found in indoor environments.

Molhave and his colleagues (1986) have studied the health effects of controlled exposure to mixtures of volatile organic compounds found in new-construction Danish homes. Subjects were healthy adults selected by means of a questionnaire survey to identify individuals who have experienced discomfort associated with indoor air quality. Subjects were exposed to three concentrations (0, 5, 25 mg/m3) of a mixture containing 22 VOCs in the climate chamber at the Institute of Hygiene, Environmental and Occupational Medicine, University of Aarhus. The composition of this mixture was based on VOCs commonly found in newly constructed Danish homes (Molhave and Moller, 1979) and is similar to the levels and types of VOCs found in U.S. homes (White, 1987). Several measures of performance and sensory irritation were obtained. Subjective ratings of sensory irritation and air quality varied significantly with VOC exposure. Results also indicated impaired memory as measured by the Digit Span Test. The implications of these results are that exposure to low level mixtures of VOCs commonly found in new or renovated buildings, levels hitherto considered to be harmless to human health, may impair the performance, productivity, comfort and well-being of workers and home-owners.

These findings provide preliminary evidence of neurotoxic effects of

exposure to complex low-level mixtures of VOCs, although further study is needed to determine the precise nature of the observed effects. For instance, are these findings limited to a particular subset of the population who dislike the odor of VOCs? Is the response psychosomatic or does low-level mixed VOC exposure produce measurable decrements in objective health endpoints? Which health endpoints are most sensitive to VOC exposure--e.g., sensory, memory pulmonary, or immunological measures? Are there other vulnerable subsets of the general population such as young children, elderly, asthmatics or persons with allergies? Are VOC exposure effects due to single constituents of the mixture or the combination of several constituents? Systematic study of these questions under controlled laboratory conditions is necessary to clarify the human health risks of exposure to indoor air pollutants. Very little evidence is currently available concerning the neurotoxic effects of low-level human exposure to complex VOC mixtures. Controlled exposure studies are also necessary before undertaking related field studies.

The type of symptoms affected by VOC exposure in the Molhave et al study has been identified as the Sick Building Syndrome (SBS) by WHO (1982). This syndrome is characterized by subjective and physiological symptoms of sensory irritation of mucosal tissue and other symptoms as shown in Table 1.

These symptoms are acute, nonspecific, and cannot be ascribed to any specific chemical(s) found in the problem environment. In the Molhave et al study, individual VOCs in the complex mixture were present at concentrations well below levels that would be expected to produce irritant effects for any single chemical in the mixture. Molhave (1986) has hypothecized that the summation of effects of exposure to the mixture, rather than any single constituent chemical, may be the cause of the effects observed in the study. Molhave (1986) has further hypothecized that the observed effects are mediated by trigeminal nerve function which is generally considered to be the neurophysiological substrate of the chemical sense.

The objective of the present study was to confirm the principal findings of the Aarhus study--i.e., increased perception of sensory irritation and

discomfort associated with exposure to a low-level complex mixture of VOCs. Molhave et al also reported an effect on digit span performance suggestive of a VOC-related impairment of short-term memory. The functional significance of the digit span finding, however, requires clarification. The observed effect could be a primary neurotoxic effect of VOC exposure or a secondary effect of sensory irritation (e.g., distraction). Digit span performance also reflects both attentional and memory processes. The present study included a battery of neurobehavioral tests designed to clarify the nature and validity of the Danish findings. Response to low-level VOC exposure was studied in normal healthy adults.

C. METHODS

C.1 Subject Selection and Characterization.

Normal healthy adult volunteers were recruited by the UNC Subject Recruitment Office (operated under EPA Contract 68-02-3800). Advertisements posted on campus and published in local newspapers were used to recruit subjects. Selection criteria based on those used in the Danish study are specified in Table 2. In brief, healthy, non- smoking Caucasion males aged 18 to 40 with no history of asthma, allergic rhinitis, cigarette use or other medical conditions were referred for physical examination and allergy testing. It should be noted that these requirements were more stringent than the Danish study which included smokers and persons up to 64 years of age. Smokers and persons over 40 years were excluded from the present study in order to minimize the variability in performance and sensory irritation that might be associated with these variables.

Exposure history was assessed by a questionnaire adapted from Molhave et al (1986). Exposure history was used to exclude individuals with significant occupational or recreational exposures that could influence neurobehavioral measures and to exclude individuals with histories of chemical sensitivity. Volunteers who met selection criteria were referred for physical examination and allergy skin testing. A standard scratch test for 18 common allergens including airborne pollens, cat and dog danders, molds and house dust was administered. Subjects with positive skin allergy tests were not included in the study in accordance with the selection criteria of Molhave et al (1986).

Payment for participation conformed to guidelines established by the EPA Clinical Research Branch. A base rate of $7 per hour and bonus for completion of the study was paid to subjects. $30 was paid to potential subjects who completed the physical examination. Subjects who qualified for participation in the study earned $84 more, depending on the number of hours devoted to training

and running in the control and exposure sessions. Subjects also received a bonus of $30 for completion of the experiment. Subjects completing all phases of the study earned a maximum of $144.

Payments were made at the end of the experiment or upon termination of participation. Although a subject could elect to discontinue the experiment at any time due to discomfort, concern or other reasons, if the subject chose to leave for non-medical reasons, only fees earned to that point were paid. On the other hand, if the investigators terminated an individual on medical or technical grounds once an exposure session had commenced, the subject(s) received full payment for that session. Subjects commuting from Durham and Raleigh were paid an additional $6 and $11, respectively, and all parking fees were paid.

To conform to the Federal Privacy Act, each subject was assigned a number at the time of physical examination. Subject privacy was maintained thereafter by exclusive use of the subject number for subject identification.

Seventy-six subjects completed the VOC study. Data from ten subjects were discarded for technical reasons including the addition of the auditory digit span test after seven subjects had been run and the accidental termination of exposure during one session with three subjects. Therefore, data from sixty-six subjects were used in statistical analyses. The mean age of subjects was 25.0 yrs. (s.d. 5.6).

C.2 Physical Facilities.

The study was carried out in the exposure facilities of the EPA Human Studies Division in Chapel Hill (Strong, 1978). The environment including temperature, humidity, light levels and pollutant concentration was continuously controlled and monitored by computer. Personnel operating this facility included EPA psychologists and technicians and a team of technical and engineering personnel from CE, Inc. who operate and maintain the facility under contract to EPA. These personnel were highly trained individuals who routinely

administer other similar protocols. A licensed physician was immediately available to the operating team during all experiments.

C.3 VOC Generation and Monitoring.

The complex VOC mixture described by Molhave et al (1986) was used in the present study with the substitution of one compound (1,1-dichloroethane for 1,2 dichlorethane). The Molhave mixture of 22 volatile organic compounds is shown in Table 3. The compounds were selected on the basis of previous Danish surveys (Molhave and Moller, 1979) including the 10 most commonly found and the 10 found in greatest concentration in indoor nonindustrial environments, but ex- cluding known carcinogens. That is, this mixture is characteristic of the chem- icals and concentrations to which residents in new Danish and American homes are often exposed. Any compounds classified by the International Agency for Research on Cancer (IARC monographs) as Group 1 (chemicals for which there is "sufficient evidence from epidemiological studies to support a causal associa- tion between the exposure and cancer") or Group 2 (chemicals that are probably carcinogenic to humans--i.e., "exposures for which there [is] at least limited evidence of carcinogenicity to humans" or "sufficient evidence in animals") were excluded.

The concentration of individual constituents of the mixture shown in Table 3 is specified in ug/m3, each of which is below the threshold limit value (TLV) for occupational exposure. TLV is the concentration of a chemical to which workers may be continuously exposed for 8 hours without adverse health effect as defined by OSHA. A system for generating and monitoring the VOC mixture equivalent to that used in the Danish study was constructed by CE, Inc. A des- scription is contained in Appendix A. Subjects were exposed to a 25 mg/m3 concentration of VOCs measured as a toluene equivalent concentration with a flame ionization detector (FID). The duration of exposure was 2.75 hours.

C.4 Equipment Readiness and Pilot Study.

Prior to initiating the main study, a pilot study was conducted to test equipment, to train the operating staff, and to check-out the protocol to insure

that the testing schedule ran smoothly. Prior to exposing subjects to the VOC mixture, extensive testing of the gas generating and monitoring system was conducted by CE to ensure that the system operated reliably and to ensure that gas concentrations did not vary by more than ±3.0% once the target level (25 mg/m3) was reached. When CE completed testing of the gas generating and monitoring equipment, two groups of three subjects (total N=6) were run through the complete protocol in order to work out any scheduling problems and to train the operating staff. Both groups were run under control (clean air) and exposure conditions as specified for the main protocol in the following sections.

C.5 Experimental Design.

Molhave et al (1986) used a repeated measures design in which each subject completed both clean air control and VOC exposure (either 5 or 25 mg/m3) conditions on the same day. Half the subjects received clean air in the morning and half in the afternoon in a counterbalanced design. There are several problems with this design including possible confounding from carry-over effects (i.e., carry-over effects on afternoon control performance from morning exposure), from practice or fatigue effects (session 1 to session 2), and from time-of-day effects (morning vs. afternoon). Carry-over effects were prevented by separating control and exposure sessions by a week or more. This separation also reduced, but did not eliminate practice effects. It also permitted each subject to complete exposure and control sessions at the same time of day, eliminating time-of-day confounding. A disadvantage was that subjects were required to return for an extra day, introducing the possibility of subject drop-out as well as other possible confounding factors such as different weather conditions or subject mood and preparedness.

To simplify the design further, only one exposure level--25 mg/m3--was run. Control and exposure sessions were administered in a double-blind manner counter-balanced across subjects similar to the design shown in Table 4A. Although the chamber could accommodate four subjects per run, subject availability limited testing on many days to less than four as shown on Table

4B.

C.6 Behavioral Battery

A battery of behavioral tests was used to assess which behavioral processes are affected by VOC exposure. The battery included the digit span test reported by Molhave et al (1986) to be impaired by VOC exposure. This test was administered in the same manner as Molhave et al--i.e., the paper-and-pencil form derived from Wechsler (1955) with auditory stimuli presented by tape recorder. Instructions for the administration and scoring of this test are contained in Appendix B. Since performance of the digit span test includes components of attention as well as memory, other behavioral tests were included to evaluate which processes are affected by VOC exposure. A main set of eight computerized behavioral tests developed by Baker and Letz (1985) and described in Appendix C was used. The tests included motor speed, memory, attention and mood. These tests were administered twice during each testing session--at the beginning and end. A secondary set of five other sensorimotor, memory and cognitive tests were administered once midway through each testing session. These tests are also described in Appendix C.

C.7 Subjective Reactions

A 25-item questionnaire related to sensory irritation, discomfort, and indoor air quality was used to obtain subjective ratings as described by Molhave et al (1986). This questionnaire is presented in Appendix D. The feeling of irritation in the eyes, nose and throat was also measured at 15-30 minute intervals using a linear potentiometer described in Appendix E. In the questionnaire subjects were asked to indicate the degree of perceived discomfort by adjusting the position of a vertical marker on a video screen by means of a joystick. The range of response varied between two well-defined extremes of items such as dryness of the nose or skin, irritation of the throat, and room noise, temperature or humidity. The linear potentiometer is a device that reduces the questionnaire to a single scale representing the collective irritation of eyes, nose and throat. The potentiometer consisted of an aluminum

box with a sliding lever which electronically and continuously recorded the comfort rating of a particular subject during the experiment.

C.8 Confirmatory and Exploratory Hypotheses.

Confirmatory and exploratory hypotheses specified a priori are stated below. Measurement variables from individual tests and questionnaires are listed in Table 5.

a. Confirmatory Hypotheses.

(1) Exposure to complex VOC mixtures will result in higher ratings of sensory irritation as measured by the linear analog rating scale (potentiometer).

(2) Exposure to complex VOC mixtures will result in impaired cognitive performance relative to clean air as follows:

i. Short-term memory as measured by span length (sum of forward and backward span lengths) in the auditory digit span test will be reduced;

ii. Coding time (msec) for symbol-digit substitution items will be longer;

iii. Selective attention, as measured by mean time/item in the switching attention test (incompatible trials) will be longer.

b. Exploratory Hypotheses.

Exposure to complex VOC mixtures will:

(3) Increase sensory irritation as indexed by questionnaire ratings;

(4) Not influence ratings of controlled climate variables--i.e., air temperature, humidity, light level and sound level;

(5) Not affect motor performance on the finger tapping test;

(6) Alter selected dimensions of mood--i.e., tension, confusion and

fatigue--as indexed by pre-post mood scale difference scores;

(7) Impair other measures of cognitive performance as indexed by continuous performance, serial digit learning and pattern memory tests.

C.9 Data Analysis Plan.

The main analyses of the experiment were done to determine if there were any VOC effects. Secondary analyses of most variables were done to determine if learning or practice effects were present and, if so, to determine the nature of those effects. In the main or confirmatory analysis were: (1) auditory digit span (forward plus backward), (2) potentiometer (comfort meter) measurements, (3) symbol-digit substitution (mean response time) and (4) switching attention test (reaction time in alternating condition). All other variables and analyses are considered as secondary or exploratory in nature.

Variables measured only once during each testing session were analyzed by a paired t-test on the two measurements for each subject. Variables with pre and post measurements were analyzed by a paired t-test on the air and VOC change (post-pre) for each subject. This analysis is equivalent to a two-way analysis of variance with subjects as one factor and treatment changes as the other factor. The two response profiles of each of the 25 questions in the comfort questionnaire and the response profiles of the comfort meter measurements were tested for parallelism using multivariate analysis of variance of repeated measures methods. If the parallelism hypothesis for a question was rejected, the three additional hypotheses were tested in order to explain the nature of the lack of parallelism. The first hypothesis compared the mid-exposure changes on air and VOC, the second hypothesis compared the post-exposure changes and the third hypothesis compared the changes from mid to post-exposure. The first three questions required either a yes or no response and were analyzed in the above manner by coding "1" for yes and "0" for no. In other words, the profile analyzed was the proportion of "yes" responses at each measurement point.

Pretest questionnaire responses were analyzed by the nonparametric McNemar test for the significance of changes. This test was used in order to answer the question of whether or not potential covariates were changing from one exposure to the other.

All variables except questionnaire and comfort meter responses were analyzed to determine if learning or practice effects were present and, if so, as far as possible, to determine the nature of those effects. For variables with pre- and post-measurements during each exposure, the exposure was ignored and the actual order of the four measurements was analyzed by fitting a first, second and third degree polynomial to the means. For variables with only one measurement during each exposure, the exposure was ignored and the first measurement was compared to the second to determine if learning effects were present.

C.10 Risks and Safeguards.

The concentrations of all volatile organic compounds used in this study were below the TLVs for occupational exposure by orders of 10 to 1000 (ACGIH, 1982). Although mucosal irritation and discomfort were reported by subjects in the study conducted by Molhave et al (1986), these effects were gone within 24 hours as indicated by follow-up questionnaires (Molhave, personal communication). Reported effects on digit span performance were marginal and transient as well. There is no evidence of any permanent adverse effect of acute VOC exposure at these levels. There is no known risk involved in the performance of the computerized behavioral battery or discomfort rating instruments.

In the unlikely event of medical emergency, a licensed physician was be present in the EPA facility at all times during the experiment. Comprehensive emergency procedures used as general practice in the operation of the facility could have been activated within seconds of the occurrence of an emergency. Emergency equipment was kept at the site of the exposure chambers at all times. Furthermore, subjects were kept under constant surveillance by trained

biomedical personnel via closed circuit TV monitoring, direct observation, and voice (intercom) communication.

D. RESULTS

D.1 Comfort Meter (Potentiometer)

Comfort meter response profiles for exposure and clean air were significantly different ($p < .001$) as shown in figure 2. That is, subjects expressed much more discomfort (irritation of mucous membranes) during VOC exposure than clean air. An abrupt divergence of comfort levels occurred when VOC exposure commenced at the 75 min. point in testing. The maximum difference in comfort levels occurred about 75 min. after exposure onset. Mean potentiometer readings (and standard errors) at each sampling point are shown in Table 6.

D.2 Symptom Questionnaire

A 25-item symptom questionnaire was administered three times during each testing session--during pre-exposure baseline, immediately after VOC build-up, and at the end of the 2.75 hr. exposure period. Mean response levels at the three measurement points for continuous items 1-22 are shown in Table 7. Significant main effects of VOC exposure (25 mg/m3) compared to clean air were found for six items including headache, odor level, eye and throat irritation, drowsiness and air quality. Figures 3 and 4 illustrate these findings. Five environmental variables (light and noise levels, temperature, humidity and air movement) were held constant during testing. Responses to control variables did not vary with exposure (Figure 5).

Different patterns of change over time in response levels were apparent for different symptoms. Further analysis of temporal patterns (Table 8) indicated that the perceived odor level increased dramatically after VOC exposure onset, but then decreased significantly with continued exposure at a constant level

(Figure 3). A similar (but inverse) pattern was observed for air quality. Headache, eye and throat irritation also increased significantly after VOC onset, but remained elevated for the duration of VOC exposure (Figure 4). Increased drowsiness, relative to clean air, was significant only at the end of exposure.

Three other questions solicited binary (yes-no) responses concerning air quality as follows:

(1) Do you feel now that staying in the chamber is comfortable?

(2) Would you be satisfied with this air quality in your own home?

(3) Would you ventilate your home more?

VOC exposure in each case elicited significant change in perceived comfort as shown in Figure 6 and Table 9. Sixty-four percent more of the subjects, for instance, indicated that they would not be satisfied with the air quality perceived after VOC exposure build-up (mid) than at the same point during clean air. A small (14%) but significant reduction in dissatisfaction occurred by the end of exposure.

D.3 Auditory Digit Span (ADS)

Six scores were derived from the ADS test including the standard measures of the longest spans recalled in forward and backward conditions and the total (forward + backward) span. Three variant measures, designated as "weighted" scores, were also obtained as described in the methods section.

A problem was encountered in the administration of ADS to some subjects who failed to reverse numbers in the backward condition. That is, numbers were written down from right-to-left on the answer sheets, enabling these subjects to complete the backward condition without mentally reversing numbers. The problem was observed in 12 subjects, despite explicit instructions and training to the contrary. Therefore, ADS results were analyzed both with and without the 12

aberrant subjects. Mean pre- and post-exposure scores are shown in Tables 10 (without 12 subjects) and 11 (all subjects). VOC exposure did not affect auditory digit span in the predicted manner. One measure (standard backward span length) varied significantly with VOC exposure, but in the wrong direction--i.e., that is, auditory digit span (backwards) was slightly longer during exposure than clean air. ADS results are shown in Figure 7.

D.4 NES Main Test Results

D.4a Finger Tapping

As predicted, finger tapping speed was not altered by VOC exposure. The mean numbers of finger taps obtained with preferred, non-preferred and alternating hands are shown in Table 12.

D.4b Visual Digit Span (VDS)

Three scores were derived from the VDS test including the longest spans recalled in forward and backward directions and the total (forward + backward) span. These scores are comparable to the standard scores obtained form the auditory digit span test. Mean pre- and post-exposure scores are shown in Table 13 and Figure 8. Forward span length increased slightly but significantly more under clean air than VOC exposure. Backward and total span lengths did not vary with exposure.

D.4c Continuous Performance Test (CPT)

Three CPT measures were analyzed--mean reaction time (RT), errors of omission, and false positives. The primary measure (RT) did not vary with VOC exposure, nor did omission errors. A marginal trend ($p = .061$) toward increased false positives was observed during VOC exposure. Mean scores are provided in Table 14 and illustrated in Figure 9.

D.4d Symbol Digit Substitution (SDS)

Two scores were obtained from the SDS test--the mean number of incorrect responses per trial, and the mean time to complete a trial (requiring nine digit substitutions). Mean scores and results are shown in Table 15. Neither score was affected by VOC exposure.

D.4e Serial Digit Learning (SDL)

Two measures were analyzed from the SDL test, a performance score described in the methods section, and a variant of the performance score in which the total number of trials to reach criterion was added to the performance score. Unlike related auditory and visual digit span tests, smaller scores indicate better performance in the SDL test. Mean scores and results are detailed in Table 16.

SDL performance was not affected by VOC exposure.

D.4f Pattern Memory (PM)

Three measures were analyzed including the mean response latency of all trials, mean response latency for correct trials only, and the mean number of correct trials. Results and means are shown in Table 17. VOC exposure did not affect pattern memory.

D.4g Switching Attention (SWATT)

Seven response-time measures were derived from the SWATT test including mean response times for three basic conditions--side, direction and the alternation of side and direction (switching). The switching condition was then broken down into four subsets of trials--side compatible, side incompatible,

direction compatible, and direction incompatible. Mean response times for each of these measures are presented in Table 18. Response times improved over the testing session (pre - post difference) for all measures during clean air. The pre - post difference was less or in the opposite direction for six of seven measures during VOC exposure, although none of the differences were statistically significant. Response times also increased markedly relative to the complexity of the type of trial--the side direction is easiest, the direction condition is more difficult, and the alternating (switching) direction condition is most difficult as shown in Figure 10.

D.4h Mood Scales

Mean scores obtained for the five mood scales during clean air and VOC exposure are shown in Table 19. Post - pre change scores differed significantly during VOC exposure on two scales (confusion and fatigue) as predicted. That is, increases in fatigue and confusion over the 4-hour testing session were greater during VOC exposure than during clean air as shown in Figure 11.

D.5 NES Secondary Test Results

D.5a Associate Learning/Recall

Two measures were obtained for this test--the total number of correct pairings over 3 trials and the number of correct pairings made during the subsequent recall trial. Means and results are shown in Table 20. Associate learning and recall were not affected by VOC exposure.

D.5b Pattern Comparison

Three measures were analyzed including the number of correct trials, mean latency for all trials, and mean latency for correct trials only. Mean scores and results are presented in Table 21. VOC exposure did not affect any pattern

comparison measures.

D.5c Simple Reaction Time (SRT)

Mean reaction-times were examined for preferred and non-preferred hands. Means and results are shown in Table 22. SRT was not altered by VOC exposure.

D.5d Grammatical Reasoning

Three measures were obtained from this test including the mean response time for individual trials, the total number of errors, and a composite score of the total number of correct responses minus the total number of errors. None of these measures was affected by VOC exposure as shown in Table 23.

D.5e Horizontal Arithmetic

Three measures were obtained including the number correct, mean response time for all trials and the mean response time for correct trials only. Slightly more problems were answered correctly during VOC exposure ($p = .031$) than during clean air as shown in Table 24.

D.6 Water Consumption

Subjects consumed slightly more water during VOC exposure (2.60 cm) than during clean air (2.36 cm), but this difference was not significant.

D.7 Learning/Practice Effects

First, Second and third degree polynomials were fitted to the four serial order means of measures from each of the NES main tests to determine whether learning or practice effects occurred beyond testing. A significant linear contrast implies that there are learning or practice effects across the two training sessions (or four serial test administrations). A significant

quadratic effect implies that the learning or practice effect is approaching or has reached asymptote. A significant cubic effect within the present design suggests that learning or practice effects occur within each testing session (pre-post comparison). The absence of linear, quadratic or cubic effects implies no learning or practice effects. Most measures showed significant serial order effects within or across testing sessions. The auditory digit span test illustrates significant linear trends for all measures (Figure 12, Table 25). The total span length measure on the Visual Digit Span Test (Figure 13, Table 26) demonstrates a clear quadratic pattern. An example of a cubic effect in the absence of linear or quadratic trends occurred on the Confusion Mood Scale (Figure 14). Response latencies on the pattern memory test exhibited a complex serial order pattern in which all three contrasts were significant (Table 27, Figure 15). Table 28 summarizes the results of polynomial contrasts for all computerized NES tests used in this study.

E. DISCUSSION

E.1 Confirmatory Hypotheses.

Four confirmatory hypothese were specified, only one of which was confirmed. As hypothesized, subjects expressed considerably more general discomfort on the linear analog rating scale of eyes, nose and throat irritation during VOC exposure than clean air. This finding is consistent with previous Danish reports (Molhave et al., 1986; Kjaergaard et al, 1989).

Other hypotheses that VOC exposure would impair cognitive performance of short-term memory on the auditory digit span test, coding time on the symbol digit substitution test, and selective attention on the switching attention test were not confirmed. Contrary to Molhave et al's (1986) report, short-term memory was not affected by VOC exposure.

E.2 Exploratory Hypotheses

Five exploratory hypotheses were specified, four of which were confirmed.

E.2a Sensory Irritation.

Symptoms of sick building syndrome, listed in Table 1, include irritation of the eyes, nose and throat; mental fatigue, and headache. Subjects expressed more irritation of eyes and throat (but not nose) during exposure to VOCs than clean air. Subjects also reported more headache and drowsiness during VOC exposure, consistent with Danish studies (Molhave et al, 1986; Kjaergaard et al, 1989). Symptom questionnaire results provide a more detailed picture of the irritant effects of VOC exposure than the general measure of discomfort provided by the linear analog rating scale. Although the potentiometer rating was defined as an index of "eye, nose and throat irritation", responses to specific symptom questions suggest that VOCs irritated the nose less than eyes and throat. This finding has implications for future VOC studies--i.e., that measures of inflammatory process in eye fluids and throat secretions may yield more useful information than in nose secretions. Failure to find a significant

increase in nose irritation is not in accord with the SBS profile, although it is consistent with Kjaergaard et al's (1989) report that VOC exposure did not produce any signs of inflammation in nasal secretions.

The most dramatic reactions to VOC exposure in the present study and in previous Danish studies were obtained on ratings of odor intensity and air quality. Subjects exposed to the 25 mg/m3 VOC mixture found the odor very strong and unpleasant. Subjects similarly reported that VOCs degrade air quality very much. Molhave et al (1988), moreover, found a systematic dose-dependent relationship of perceived odor intensity and air quality at VOC exposure levels of 3, 8, and 25mg/m3.

The strong and unmistakable odor of the VOC mixture poses a methodologic challenge--i.e., VOCs and clean air cannot be administered to subjects in a double-blind manner. Subjects know unequivocally when exposure begins. This problem was reduced by using a counterbalanced design. The rapid habituation of olfactory sensation also helps to mitigate this problem. Results of the present study, for instance, indicate that perceived odor intensity decreased at the end of the testing period, while eye, throat, headache, fatigue and confusion scores either increased or remained elevated during the 2.75 hour exposure period. The irritant effects of VOC exposure thought to be mediated by the trigeminal nerve (Molhave, 1986), can thus be distinguished from olfactory response over time. Further study is needed to characterize in detail the time course of olfactory and trigeminal response to VOCs.

E.2b Controlled Climate Variables

It was further hypothesized that ratings of five climate variables (air temperature, humidity, light and noise levels, and air flow), which were held constant throughout testing, would not vary with VOC exposure. This hypothesis was confirmed, providing construct validity to the symptom questionnaire.

E.2c Motor Performance.

The finger tapping test provides a simple, straightforward measure of motor

performance. Since motor dysfunction has not been associated with VOC exposure, we predicted no effects on finger tapping. This hypothesis was confirmed.

E.2d Mood Scale Alterations.

Pre-post differences on three mood scales--tension, confusion and fatigue--associated with VOC exposure were hypothesized. This hypothesis was confirmed for confusion and fatigue, but not tension. These findings are consistent with SBS syndrome as well as the drowsiness item on the symptom questionnaire. The lack of effect on the tension and anger scales is of some interest, particularly in view of the perceived increase in discomfort and sensory irritation. Many constituents of the mixture are organic solvents with known anesthetic or CNS depressant properties--e.g., n-butylacetate, 1-1-dichloroethane, n-hexane, and p-xylene (Anger and Johnson, 1985). The anesthetic or narcotic effects of the solvents may account for the absence of tension or anger in subjects during VOC exposure.

E.2e Cognitive Performance.

The final exploratory hypothesis concerning the impairment of performance on three different tests of cognitive performance (continuous performance test, serial digit learning and pattern memory) was not confirmed. The results of all memory, sensorimotor and other types of cognitive tests were very consistent. None of these tests showed any convincing evidence that VOC exposure impaired performance, despite marked subjective reactions on the symptom questionnaire and comfort rating scale. Nor is this finding particularly surprising in view of the low aggregate exposure level (7 ppm toluene equivalent) of the VOC mixture. Neurobehavioral effects have seldom been observed below 300 ppm toluene (Johnson et al, 1987). Concentrations of individual chemicals in the mixture were below TLVs by factors of 10 to 100 or more.

Molhave et al (1986) reported a small reduction in digit span during VOC exposure. The consistent negative results on fourteen neurobehavioral tests argue rather persuasively against any functional impairment in healthy young adult males exposed to this concentration (25 mg/m3) of volatile organic

compounds. Exposure and clean air sessions were run in the morning and and afternoon of the same day in the original Danish study, giving rise to possible confounding from exposure carry-over effects, practice or fatigue effects, and time-of-day effects. Modifications in the experimental design, to mitigate these confounding factors render the present results more reliable than the original study.

On the other hand, several important differences in the subject samples used in the two studies could possibly account for the discrepant digit span findings. (1) Molhave et al carefully selected chemically sensitive subjects with documented histories of indoor climate problems. Chemically sensitive subjects were excluded from the present study. (2) The range of ages in the Danish study (18-60 years) was much wider than the present study (19-39 years). Older subjects could be more sensitive than younger subjects to VOC exposure. (3) Finally, the Danish study included equal numbers of males and females. Maizlich et al (1987) have shown that females perform more poorly than males on many NES tests. Whether cognitive performance is more susceptible to impairment by VOC exposure in women then men, in older than younger subjects, and in chemically sensitive compared to normal healthy subjects are questions that require further study.

E.3 Effects of Practice and Learning

The question of practice or learning effects is an important concern in repeated-measures studies employing neurobehavioral tests. Such effects could exaggerate or obscure effects of chemical exposure if not controlled properly in the experimental design. It is also of considerable interest to the research community to characterize the effects of practice and learning in a widely used neurotoxicity testing system. For the present discussion the terms "practice" and "learning" will be used synonymously. Although the study was not specifically designed to examine practice effects, the study provided a convenient and extensive dataset to evaluate this question.

Nine tests were administered twice on each of two test days, yielding four

replications. Test days were separated by at least one week. Practice effects were evaluated by testing for linear, quadratic and cubic trends in the data arrayed in the serial order of presentation. As noted previously, a significant linear trend implies extended practice effects across the four test administrations, quadratic effects imply that practice effects approach or reach asymptote levels, and cubic effects imply transient practice effects (within a testing session).

Results of polynomial tests for serial order effects are summarized in Table 28 including data on nine tests repeated four times. Evidence of extended practice effects (significant linear trends) were found on five tests--auditory and visual digit span, continuous performance, symbol digit substitution, and switching attention tests. Results of three secondary NES tests (associate learning, pattern comparison, and grammatical reasoning tests), administered once during each testing session, also suggest extended practice effects. Only one of five mood scales (tension) exhibited a significant linear trend. Tests which do not appear to have extended practice effects include finger tapping, serial digit learning, other mood scales, simple reaction time, and horizontal addition. Finger tapping and two mood scales (fatigue and confusion), however, showed significant cubic trends which imply within-session effects, but no between-session effect. Mood scales, in particular, are designed to assess short-term subjective reactions to experimental variables. Fatigue and confusion scales, if valid, should vary over a demanding task and then return to previous values after resting or at the beginning of another testing session. Significant quadratic effects were observed in two tests--visual digit span and pattern memory--and marginal quadratic trends were found for some variables in serial digit learning, switching attention, and the tension scale. All three trends occurred in the pattern memory test.

The implication of the serial order analysis is that practice or learning effects occur in the performance of most neurobehavioral tests commonly used in neurotoxicity testing of humans. It should be noted that these effects were observed despite an initial training session. Data from the training session were not included in the present analysis because the length and complexity of

some tests varied on training and testing days. However, a single training session does not appear to be adequate to eliminate practice/learning effects on most NES tests. Further parametric studies need to be done to systematically evaluate the practice/learning characteristics of each NES test. Task complexity, length of task and interest trial interval must be carefully assessed in order to determine optimal parameters for the use of NES tests in repeated-measures studies in the laboratory as well as in the field.

14. REFERENCES

American Conference of Government Industrial Hygienists. Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environ- ment with Intended Changes for 1982. ACGIH Publ. Office, Cincinnati, 1982.

Bach B, Molhave L, Pedersen OF. Human reactions during controlled exposures to low concentrations of organic gases and vapors known as normal indoor air pollutants: Performance tests. In Berglund et al (eds) Indoor Air, Vol 3, Sensory and Hyperreactivity Reactions to Sick Buildings. Swedish Council for Building Research, Stockholm, 1984, pp397-401.

Hathaway SR, McKinley JC. The Minnesota Multiphasic Personality Inventory. The Psychological Corporation, 304 East 45th St, New York, NY 10017, 1966.

Hollingshead AB. Two-factor index of social position. Unpublished ms., Yale University, 1957 (Available from the author, 1965 Yale Station, New Haven, CT 06520).

IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Volumes 1-41, Lyon, 1971-1986.

Johnson BL (ed). Prevention of Neurotoxic Illness in Working Populations. Wiley, New York, 1987.

Kjaergaard S, Molhave L, Pedersen O.F. Human reactions to a mixture of indoor air volatile organic compounds. Environment Int., 1989 (in press).

Letz R, Baker EL. Computer-administered neurobehavioral testing: On defining its limitatins. In: Environmental Health, Doc 3, World Health Organization, Copenhagen, 1985:158-162.

Maizlich N, Schenker M, Weisskopf C, Seiber J, Samuels S. A behavioral evaluation of pest control workers with short-term, low-level exposure to the organophosphate Diazinon. Am J Indus Med, 1987, 12:153-172.

Melius J, Wallingford K, Carpenter J, Keenlyside R. Indoor air quality: the NIOSH experience. Am Conf Indus Hyg, Rep 10, 1984: 3-7.

Molhave L. Indoor air quality in relation to sensory irritation due to volatile organic compounds. ASHRAE Transactions, Vol 92(1), paper 2954, Dec 1986.

Molhave L, Bach B, Pedersen OF. Human reactions during controlled exposures to low concentrations of organic gases and vapors known as normal indoor air pollutants. In Berglund et al (eds) Indoor Air, Vol 3, Sensory and Hyperreactivity Reactions to Sick Buildings. Swedish Council for Building Research, Stockholm, 1984, pp431-436.

Molhave L, Bach B, Pedersen OF. Human reactions to low concentrations of volatile organic compounds. Environment Int., 1986, 12: in press.

Molhave L, Jensen JG, Larsen S. Acute afnd subacute subjective reactions to volatile organic air pollutants. Unpublished Report, Inst. Environ. Occup. Med., Univ. of Aarhus, Denmark, Dec. 1988.

Molhave L, Moller J. The atmospheric environment in modern Danish dwellings-Measurements in 39m flats. in Indoor Climate, P Fanger and O Valbjorn (eds), SBI, Horsholm, Denmark, 1979, pp171-186.

National Research Council, Committee on Indoor Pollutants. Indoor Pollutants. National Academy Press, Washington, DC, 1981.

Strong AA. Description of the CLEANS Human Exposure System. EPA-600/1-78-064, Health Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC, Nov 1978.

Wechsler D. Wechsler Adult Intelligence Scale Manual. Psychological Corporation, New York, 1955.

White JR. A Review of Indoor Air Contaminants and Recommendations for a "Typical" Indoor Air Mixture. Internal Report, Air and Energy Engineering Laboratory, U.S. Environmental Protection Agency, Research Triangle, 1987.

World Health Organization. Indoor Air Quality Research. EURO Reports 103, Stockholm, 1986.

TABLE 1. SYMPTOMS OF SICK BUILDING SYNDROME (WHO, 1982)

Irritation of eye, nose and throat
Dry mucous membrane and skin
Erythema
Mental fatigue, headache
Airway infections, cough
Hoarseness of voice, wheezing
Nonspecific hyperreactivity reactions
Nausea, dizziness

TABLE 2. SUBJECT SELECTION CRITERIA

Age: 18-40 years
Race: Caucasion
Gender: Male
Non smokers
No pre-existing diseases or abnormal conditions such as:
*chronic airway disease
*cardiac disease
*Asthma
*Chronic bronchitis
*tuberculosis
*Psychiatric disorder
*Neurological disorder
*Skin disease
*Chronic eye disease
*Obesity
*Cancer or other severe disease
*Alcohol or Drug Addiction
*IgE Atopy (negative skin test to common agents)
Native language must be English
Subjects must be able to perform tasks without difficulty
Normal psychological profile as determined by MMPI

TABLE 3. MOLHAVE et al (1986) VOC MIXTURE

No.	Compound	Ratio	conc. (ug/m3)*
1	n-Hexane	1	825
2	n-Nonane	1	825
3	n-Decane	1	825
4	n-Undecane	0.1	75
5	1-Octene	0.01	8
6	1-Decene	1	825
7	Cyclohexane	0.1	75
8	3-Xylene	10	8250
9	Ethylbenzene	1	825
10	1,2,4-Trimethylbenzene	0.1	75
11	n-Propylbenzene	0.1	75
12	a-Pinene	1	825
13	n-Pentanal	0.1	75
14	n-Hexanal	1	825
15	Iso-propanol	0.1	75
16	n-Butanol	1	825
17	2-Butanone (MEK)	0.1	75
18	3-Methyl-3-Butanone	0.1	75
19	4-Methyl-2-Pentanone	0.1	75
20	n-Butylacetate	10	8250
21	Ethoxyethylacetate	1	825
22	1,1-Dichloroethane	1	825

*Based on a mixture with a total concentration of 25 mg/m3

TABLE 4. EXPERIMENTAL DESIGN

A.

TREATMENT	SESSION 1	SESSION 2
A	0	25
B	25	0

B.

No. of Subjects in Chamber	Frequency of Occurrence during Testing
1	20
2	23
3	15
4	10

TABLE 5. MEASUREMENT VARIABLES

A. MAIN NES TESTS

TEST	MEASURE	C/E*
Finger Tapping	#Taps for preferred, non preferred, and alternating condition	E
Visual Digit Span	Total span length (forward+backward)	E
	Forward span length	E
	Backward span length	E
Continuous Performance Test	Mean Reaction Time	E
	#Misses	E
	#False Alarms	E
Symbol Digit Substitution	Mean msec/digit	C
	#errors	E
Serial Digit Learning	#trials attempted + score	E
Pattern Memory	Mean msec/trial	E
	#correct	E
Switching Attention	Mean msec/side condition	E
	Mean msec/direction condition	E
	Mean msec/switching condition	C
Mood Scales	Tension	E
	Depression	E
	Anger	E
	Fatigue	E
	Confusion	E

TABLE 5 (cont.)

B. SECONDARY NES TESTS

TEST	MEASURE	C/E
Associate Learning	# Correct (trials 1-3)	E
Associate Recall	# pairs correctly recalled	E
Pattern Comparison	mean latency of trials 2-25, excluding incorrect trials	E
	# trials correct	E
Simple Reaction Time	mean RT for preferred hand (P2-P5) and non preferred hand (N6-N9), excluding block 1	E
Grammatical Reasoning	mean response time	E
	# errors	E
Horizontal Arithmetic	# correct	E
	mean response time	E

C. OTHER TESTS

Auditory Digit Span	total span length (Fwd + Bwd)	C
	forward span length	E
	backward span length	E
Comfort Scale (Potentiometer)	difference profile between VOC exposure and clean air	C
Symptom Questionaire	difference between VOC exposure and clean air for individual items	E

*C=Conformity, E=Exploratory Measures

1

TABLE 6

MEAN POTENTIOMETER READING
BY EXPOSURE AND TIME

EXPOSURE	TIME (MINUTES)	MEAN*	S.E.
AIR	0	.048	.017
	15	.059	.020
	30	.234	.045
	45	.235	.045
	60	.235	.045
	75	.310	.056
	90	.321	.055
	105	.361	.056
	120	.362	.056
	135	.438	.069
	150	.461	.070
	165	.531	.081
	180	.467	.077
	195	.476	.078
	210	.586	.097
	225	.572	.093
	240	.570	.094
VOC	0	.103	.033
	15	.106	.033
	30	.373	.055
	45	.382	.054
	60	.380	.054
	75	.570	.074
	90	.921	.096
	105	1.084	.100
	120	1.136	.106
	135	1.277	.117
	150	1.303	.123
	165	1.131	.115
	180	1.166	.116
	195	1.178	.118
	210	1.223	.123
	225	1.222	.131
	240	1.223	.131

* N=63

Ho: $F(16,47) = 3.98$ ($P<.001$)

TABLE 7

QUESTIONNAIRE

QUESTION	TIME	AIR MEAN(#)	AIR S.E.	VOC MEAN(#)	VOC S.E.	F* (P)
1. BODY/SKIN IRRITATION	PRE	1.77	0.51	1.73	0.48	
	MID	3.35	0.73	5.26	0.90	1.71
	POST	5.18	0.80	6.39	0.92	(.190)
2. NOISE LEVEL	PRE	11.48	0.76	10.88	0.75	
	MID	12.91	0.82	13.45	0.81	1.37
	POST	13.80	0.85	14.09	0.88	(.261)
3. EYES DRY / WATERY	PRE	12.71	0.36	13.30	0.34	
	MID	12.23	0.45	12.39	0.59	0.47
	POST	11.30	0.56	11.24	0.60	(.626)
4. HEADACHE	PRE	2.00	0.61	1.64	0.48	
	MID	2.12	0.53	5.05	0.82	9.52
	POST	3.41	0.76	6.97	1.04	(<.001)
5. FACIAL SKIN TEMPERATURE	PRE	14.00	0.37	14.53	0.39	
	MID	12.30	0.55	12.82	0.63	2.05
	POST	11.33	0.63	13.21	0.60	(.138)
6. SLUGGISHNESS	PRE	6.33	0.85	5.70	0.84	
	MID	8.27	0.95	8.70	0.94	2.42
	POST	9.83	1.09	11.71	1.10	(.098)
7. ODOR LEVEL	PRE	8.73	0.95	8.86	0.99	
	MID	6.53	0.89	21.68	0.80	77.90
	POST	6.68	0.91	17.77	1.09	(<.001)
8. EYE IRRITATION	PRE	2.56	0.57	3.70	0.76	
	MID	5.21	0.87	9.68	1.04	4.13
	POST	7.59	0.97	10.71	1.13	(.021)
9. BODY TEMPERATURE	PRE	14.03	0.46	13.86	0.49	
	MID	11.05	0.56	11.58	0.62	1.84
	POST	10.05	0.66	11.55	0.64	(.167)
10. LIGHT INTENSITY	PRE	17.11	0.44	17.44	0.50	
	MID	17.35	0.48	17.68	0.52	0.00
	POST	18.08	0.55	18.42	0.53	(.999)
11. COUGHING	PRE	1.38	0.41	1.14	0.41	
	MID	0.94	0.32	2.06	0.57	2.31
	POST	1.05	0.37	1.82	0.55	(.108)

* N=66

* 2 & 64 Degrees of Freedom

TABLE 7
(Con t)
QUESTIONNAIRE

QUESTION	TIME	AIR MEAN(#)	AIR S.E.	VOC MEAN(#)	VOC S.E.	F* (P)
12. FACE IRRITATION	PRE	1.70	0.46	2.36	0.56	
	MID	3.35	0.76	4.33	0.79	0.08
	POST	4.55	0.84	5.17	0.86	(.924)
13. HUMIDITY	PRE	11.62	0.56	12.24	0.54	
	MID	11.38	0.61	12.50	0.62	0.24
	POST	11.44	0.65	12.24	0.60	(.784)
14. AIR MOVEMENT	PRE	17.86	0.67	17.88	0.65	
	MID	19.79	0.59	19.41	0.62	0.50
	POST	20.09	0.62	20.23	0.57	(.612)
15. NOSE IRRITATION	PRE	4.33	0.80	5.12	0.85	
	MID	5.26	0.89	7.77	0.97	1.16
	POST	6.85	1.03	9.41	1.11	(.319)
16. TEMPERATURE	PRE	10.82	0.42	10.47	0.35	
	MID	8.61	0.47	8.36	0.46	0.60
	POST	7.70	0.53	7.95	0.44	(.550)
17. TIRED SLEEPY	PRE	6.97	0.89	5.98	0.90	
	MID	8.79	1.02	8.08	0.91	4.38
	POST	10.45	1.02	12.15	1.05	(.017)
18. SKIN, BODY MOIST/DRY	PRE	12.88	0.37	13.02	0.42	
	MID	12.03	0.60	12.00	0.42	0.36
	POST	11.76	0.56	12.24	0.47	(.696)
19. THROAT IRRITATION	PRE	2.48	0.60	1.71	0.46	
	MID	3.92	0.79	5.65	0.94	4.41
	POST	4.45	0.92	6.18	1.00	(.016)
20. AIR QUALITY	PRE	11.00	0.74	10.74	0.77	
	MID	11.59	0.80	19.98	0.70	32.86
	POST	11.52	0.87	18.36	0.80	(<.001)
21. FACIAL SKIN MOIST/DRY	PRE	12.65	0.51	12.45	0.49	
	MID	12.23	0.56	12.17	0.52	0.08
	POST	11.86	0.59	11.53	0.56	(.922)
22. CONCENTRATION	PRE	2.42	0.59	2.26	0.56	
	MID	2.55	0.55	3.42	0.69	1.75
	POST	3.20	0.66	4.03	0.75	(.183)

* N=66
* 2 & 64 Degrees of Freedom

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TABLE 8
ANALYSIS OF QUESTIONS
4, 7, 8, 17, 19, AND 20

QUESTION	CONTRAST (*)	CONTRAST MEAN	F(**)	P
4. HEADACHE	1	3.29	16.04	<.001
	2	3.92	15.99	<.001
	3	0.63	0.70	0.406
7. ODOR LEVEL	1	15.02	153.16	<.001
	2	10.96	79.04	<.001
	3	-4.06	12.79	<.001
8. EYE IRRITATION	1	3.33	8.24	0.006
	2	1.98	2.34	0.131
	3	-1.35	1.01	0.318
17. TIRED / SLEEPY	1	0.28	0.05	0.815
	2	2.69	4.65	0.035
	3	2.41	7.80	0.007
19. THROAT IRRITATION	1	2.50	6.73	0.012
	2	2.50	6.84	0.011
	3	0.00	0.00	0.999
20. AIR QUALITY	1	8.65	66.47	<.001
	2	7.10	39.92	<.001
	3	-1.55	5.30	0.024

*1: Change to mid on VOC - Change to mid on AIR
2: Change to post on VOC - Change to post on AIR
3: Contrast 2 - Contrast 1
** 1 and 65 Degrees of Freedom

TABLE 9

QUESTIONNAIRE
(YES-NO QUESTIONS)

QUESTION	TIME	AIR PROP. "YES"	AIR S.E.	VOC PROP. "YES"	VOC S.E.	F* (P)
23	PRE	0.95	0.03	0.97	0.02	
	MID	0.92	0.03	0.62	0.06	15.19
	POST	0.80	0.05	0.59	0.06	(<.001)
24	PRE	0.79	0.05	0.79	0.05	
	MID	0.73	0.06	0.09	0.04	44.68
	POST	0.74	0.05	0.23	0.05	(<.001)
25	PRE	0.35	0.06	0.33	0.06	
	MID	0.38	0.06	0.83	0.05	22.35
	POST	0.36	0.06	0.73	0.06	(<.001)

N=66
* 2 & 64 Degrees of Freedom

TABLE 9A

QUESTIONNAIRE
(YES-NO QUESTIONS)

QUESTION	CONTRAST (*)	CONTRAST MEAN	F(**)	P
23	1	-0.32	26.62	<.001
	2	-0.23	12.60	<.001
	3	0.09	1.51	0.223
24	1	-0.64	90.14	<.001
	2	-0.51	50.63	<.001
	3	0.13	4.84	0.031
25	1	0.47	42.18	<.001
	2	0.39	28.59	<.001
	3	-0.08	2.03	0.159

*1: Change to mid on VOC - Change to mid on AIR
 2: Change to post on VOC - Change to post on AIR
 3: Contrast 2 - Contrast 1
** 1 and 65 Degrees of Freedom

TABLE 10
AUDITORY DIGIT SPAN
(WITHOUT 12 SUBJECTS)

TEST	TRT	TIME	MEAN*	S.E.	CHANGE (POST -PRE)	P-value **
FORWARD (STANDARD)	AIR	PRE	7.85	0.14		
		POST	8.09	0.13	0.24	
	VOC	PRE	7.89	0.15		0.869
		POST	8.09	0.14	0.20	
BACKWARD (STANDARD)	AIR	PRE	7.43	0.11		
		POST	7.24	0.15	-0.19	
	VOC	PRE	7.22	0.13		0.028
		POST	7.54	0.11	0.31	
TOTAL (STANDARD)	AIR	PRE	15.28	0.22		
		POST	15.33	0.22	0.06	
	VOC	PRE	15.11	0.24		0.132
		POST	15.63	0.21	0.52	
FORWARD (WEIGHTED)	AIR	PRE	60.61	1.99		
		POST	62.74	1.71	2.13	
	VOC	PRE	60.96	1.95		0.638
		POST	61.91	2.04	0.94	
BACKWARD (WEIGHTED)	AIR	PRE	53.43	1.61		
		POST	54.43	1.73	1.00	
	VOC	PRE	53.81	1.74		0.096
		POST	58.59	1.69	4.78	
TOTAL (WEIGHTED)	AIR	PRE	114.04	3.31		
		POST	117.17	2.89	3.13	
	VOC	PRE	114.80	3.32		0.462
		POST	120.50	3.14	5.70	

* N=54 for all means
** Ho: Change on VOC - Change on AIR = 0

TABLE 11
AUDITORY DIGIT SPAN
(ALL SUBJECTS)

TEST	TRT	TIME	MEAN*	S.E.	CHANGE (POST -PRE)	P-value **
FORWARD (STANDARD)	AIR	PRE	7.80	0.13		
		POST	8.11	0.12	0.30	
	VOC	PRE	7.86	0.13		0.503
		POST	8.03	0.13	0.17	
BACKWARD (STANDARD)	AIR	PRE	7.17	0.15		
		POST	7.17	0.13	0.00	
	VOC	PRE	7.14	0.13		0.259
		POST	7.38	0.14	0.24	
TOTAL (STANDARD)	AIR	PRE	14.97	0.24		
		POST	15.27	0.20	0.30	
	VOC	PRE	15.00	0.22		0.721
		POST	15.41	0.22	0.41	
FORWARD (WEIGHTED)	AIR	PRE	59.95	1.72		
		POST	62.47	1.54	2.52	
	VOC	PRE	60.62	1.76		0.481
		POST	61.58	1.90	0.95	
BACKWARD (WEIGHTED)	AIR	PRE	50.95	1.82		
		POST	50.20	1.68	2.24	
	VOC	PRE	52.52	1.58		0.208
		POST	54.47	1.65	4.95	
TOTAL (WEIGHTED)	AIR	PRE	110.91	3.20		
		POST	115.67	2.69	4.76	
	VOC	PRE	113.15	3.02		0.715
		POST	119.05	3.00	5.89	

* N=66 for all means
** Ho: Change on VOC - Change on AIR = 0

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TABLE 12
FINGER TAPPING

TEST	TRT	TIME	MEAN*	S.E.	CHANGE (POST -PRE)	P-value **
NUMBER TAPS (PREFERRED HAND)	AIR	PRE	116.6	1.9		
		POST	113.3	1.9	-3.3	
	VOC	PRE	114.1	1.8		0.213
		POST	113.5	1.9	-0.6	
NUMBER TAPS (NON-PREFERRED HAND)	AIR	PRE	106.3	1.7		
		POST	102.7	1.4	-3.6	
	VOC	PRE	104.7	1.5		0.386
		POST	102.1	1.5	-2.6	
NUMBER TAPS (ALTER-NATING)	AIR	PRE	101.0	1.8		
		POST	99.9	1.3	-1.1	
	VOC	PRE	102.4	2.3		0.135
		POST	98.9	1.9	-3.5	

* N=66 for all means
** Ho: Change on VOC - Change on AIR = 0

TABLE 13
VISUAL DIGIT SPAN

TEST	TRT	TIME	MEAN*	S.E.	CHANGE (POST -PRE)	P-value **
LONGEST FORWARD SPAN LENGTH	AIR	PRE	7.68	0.17		
		POST	8.20	0.16	0.52	
	VOC	PRE	7.97	0.17		0.030
		POST	8.06	0.16	0.09	
LONGEST BACKWARD SPAN LENGTH	AIR	PRE	7.53	0.21		
		POST	7.62	0.20	0.09	
	VOC	PRE	7.59	0.21		0.512
		POST	7.83	0.21	0.24	
TOTAL	AIR	PRE	15.21	0.34		
		POST	15.82	0.32	0.61	
	VOC	PRE	15.56	0.34		0.416
		POST	15.89	0.32	0.33	

* N=66 for all means
** Ho: Change on VOC - Change on AIR = 0

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TABLE 14
CONTINUOUS PERFORMANCE TASK

TEST	TRT	TIME	MEAN*	S.E.	CHANGE (POST -PRE)	P-value **
MEAN REACTION TIME	AIR	PRE	376.3	4.23		
		POST	380.4	4.08	4.1	
	VOC	PRE	375.5	4.14		0.156
		POST	383.7	4.37	8.2	
TOTAL OMISSION ERRORS	AIR	PRE	0.26	0.11		
		POST	0.48	0.14	0.22	
	VOC	PRE	0.26	0.08		0.406
		POST	0.35	0.09	0.09	
TOTAL FALSE POSITIVES	AIR	PRE	0.91	0.14		
		POST	0.88	0.19	-0.03	
	VOC	PRE	0.74	0.14		0.061
		POST	1.20	0.15	0.46	

* N=66 for all means
** Ho: Change on VOC - Change on AIR = 0

TABLE 15
SYMBOL-DIGIT SUBSTITUTION

TEST	TRT	TIME	MEAN*	S.E.	CHANGE (POST -PRE)	P-value **
MEAN NUMBER CORRECT	AIR	PRE	.028	.008		
		POST	.027	.009	-0.001	
	VOC	PRE	.034	.007		0.812
		POST	.029	.009	-0.005	
MEAN TIME	AIR	PRE	15.05	0.27		
		POST	14.61	0.27	-0.44	
	VOC	PRE	14.94	0.24		0.954
		POST	14.50	0.25	-0.44	

* N=66 for all means
** Ho: Change on VOC - Change on AIR = 0

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TABLE 16
SERIAL DIGIT LEARNING

TEST	TRT	TIME	MEAN*	S.E.	CHANGE (POST -PRE)	P-value **
SCORE	AIR	PRE	2.55	0.28		
		POST	2.48	0.34	-0.07	
	VOC	PRE	2.70	0.27		0.548
		POST	2.89	0.34	0.19	
SCORE + NUMBER OF TRIALS	AIR	PRE	6.45	0.44		
		POST	6.30	0.53	-0.15	
	VOC	PRE	6.80	0.45		0.539
		POST	7.06	0.52	0.26	

* N=66 for all means
** Ho: Change on VOC - Change on AIR = 0

TABLE 17
PATTERN MEMORY

TEST	TRT	TIME	MEAN*	S.E.	CHANGE (POST -PRE)	P-value **
LATENCY (ALL TRIALS)	AIR	PRE	5.21	0.18		
		POST	4.29	0.14	-0.92	
	VOC	PRE	5.08	0.16		0.359
		POST	4.31	0.14	-0.77	
LATENCY (CORRECT TRIALS ONLY)	AIR	PRE	4.98	0.17		
		POST	4.02	0.13	-0.96	
	VOC	PRE	4.82	0.15		0.157
		POST	4.08	0.14	-0.74	
NUMBER CORRECT	AIR	PRE	23.3	0.20		
		POST	22.7	0.23	-0.6	
	VOC	PRE	23.2	0.17		0.856
		POST	22.7	0.24	-0.5	

* N=66 for all means
** Ho: Change on VOC - Change on AIR = 0

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TABLE 18
SWITCHING ATTENTION TEST

TEST	TRT	TIME	MEAN*	S.E.	CHANGE (POST -PRE)	P-value
SIDE CONDITION	AIR	PRE	319.5	6.2		
		POST	315.7	7.1	-3.8	
	VOC	PRE	320.3	6.6		0.611
		POST	321.1	6.7	0.8	
DIRECTION CONDITION	AIR	PRE	432.2	6.9		
		POST	428.0	8.4	-4.2	
	VOC	PRE	430.9	7.7		0.473
		POST	419.9	7.7	-11.0	
SWITCHING CONDITION	AIR	PRE	489.3	13.8		
		POST	474.9	13.8	-14.4	
	VOC	PRE	485.9	16.6		0.341
		POST	483.4	15.4	-2.5	
SWITCHING-SIDE COMPAT.	AIR	PRE	426.4	14.7		
		POST	416.4	14.6	-10.0	
	VOC	PRE	410.6	14.5		0.337
		POST	414.6	15.0	4.0	
SWITCHING-SIDE INCOMPAT.	AIR	PRE	444.1	15.4		
		POST	427.5	17.0	-16.6	
	VOC	PRE	446.0	22.1		0.561
		POST	438.7	18.8	-7.3	
SWITCHING DIRECTION COMPAT.	AIR	PRE	550.4	14.0		
		POST	537.0	13.6	-13.4	
	VOC	PRE	551.5	17.6		0.321
		POST	553.7	16.9	2.2	
SWITCHING DIRECTION INCOMPAT.	AIR	PRE	536.1	13.8		
		POST	518.8	13.2	-17.3	
	VOC	PRE	535.6	15.6		0.532
		POST	526.8	14.4	-8.8	

* N=66 for all means
** Ho: Change on VOC - Change on AIR = 0

TABLE 19
MOOD SCALE

TEST	TRT	TIME	MEAN*	S.E.	CHANGE (POST -PRE)	P-value
TENSION SCORE	AIR	PRE	1.97	0.07		
		POST	1.89	0.06	-0.08	
	VOC	PRE	1.94	0.08		0.153
		POST	1.98	0.08	0.04	
DEPRESSION SCORE	AIR	PRE	1.57	0.05		
		POST	1.58	0.06	0.01	
	VOC	PRE	1.50	0.05		0.197
		POST	1.57	0.05	0.07	
ANGER SCORE	AIR	PRE	1.18	0.04		
		POST	1.20	0.05	0.02	
	VOC	PRE	1.23	0.06		0.722
		POST	1.22	0.04	-0.01	
FATIGUE SCORE	AIR	PRE	2.68	0.09		
		POST	2.75	0.09	0.07	
	VOC	PRE	2.58	0.09		0.045
		POST	2.82	0.08	0.24	
CONFUSION SCORE	AIR	PRE	1.94	0.06		
		POST	1.97	0.06	0.03	
	VOC	PRE	1.93	0.07		0.026
		POST	2.10	0.08	0.17	

* N=66 for all means
** Ho: Change on VOC - Change on AIR = 0

TABLE 20
ASSOCIATIVE LEARNING

TEST	TRT	MEAN*	S.E.	DIFFERENCE: VOC-AIR	P-value **
TOTAL CORRECT	AIR	21.15	0.62		
	VOC	22.06	0.55	0.91	0.132
RECALL	AIR	7.94	0.17		
	VOC	8.02	0.21	0.08	0.747

* N=66 for all means
** Ho: VOC - AIR = 0

TABLE 21
PATTERN COMPARISON

TEST	TRT	MEAN*	S.E.	DIFFERENCE: VOC-AIR	P-value **
NUMBER TRIALS CORRECT	AIR	24.80	0.06		
	VOC	24.85	0.05	0.05	0.581
LATENCY (ALL TRIALS)	AIR	3.07	0.09		
	VOC	3.07	0.08	0.00	0.968
LATENCY (CORRECT ONLY)	AIR	3.07	0.09		
	VOC	3.07	0.08	0.00	0.969

* N=66 for all means
** Ho: VOC - AIR = 0

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TABLE 22
SIMPLE REACTION TIME

TEST	TRT	MEAN*	S.E.	DIFFERENCE: VOC-AIR	P-value **
REACTION TIME (PREFERRED HAND)	AIR	244.3	3.38		
	VOC	246.4	3.41	2.1	0.455
REACTION TIME (NON-PREFERRED HAND)	AIR	253.7	3.91		
	VOC	254.3	3.54	0.6	0.862

* N=66 for all means
** Ho: VOC - AIR = 0

TABLE 23
GRAMMATICAL REASONING

TEST	TRT	MEAN*	S.E.	DIFFERENCE: VOC-AIR	P-value **
MEAN RESPONSE TIME	AIR	3396	96		
	VOC	3375	101	-21	0.737
SUM OF ERRORS	AIR	6.7	0.9		
	VOC	6.2	0.9	-0.5	0.482
SCORE	AIR	54.5	1.5		
	VOC	54.9	1.5	0.4	0.694

* N=66 for all means
** Ho: VOC - AIR = 0

TABLE 24
HORIZONTAL ADDITION

TEST	TRT	MEAN*	S.E.	DIFFERENCE: VOC-AIR	P-value **
NUMBER CORRECT	AIR	58.5	0.18		
	VOC	58.9	0.11	0.4	0.031
RESPONSE TIME (ALL TRIALS)	AIR	3.26	0.09		
	VOC	3.25	0.08	-0.01	0.766
RESPONSE TIME (CORRECT ONLY)	AIR	3.25	0.09		
	VOC	3.24	0.08	-0.01	0.806

* N=66 for all means
** Ho: VOC - AIR = 0

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TABLE 25
AUDITORY DIGIT SPAN
(ALL SUBJECTS)

TEST	ORDER	MEAN*	S.E.	CONTRAST	P-value
FORWARD (STANDARD)	1	7.74	0.13		
	2	8.06	0.13	LINEAR	0.042
	3	7.92	0.13	QUADRATIC	0.379
	4	8.08	0.12	CUBIC	0.081
BACKWARD (STANDARD)	1	7.03	0.15		
	2	7.11	0.14	LINEAR	0.002
	3	7.27	0.13	QUADRATIC	0.644
	4	7.44	0.13	CUBIC	0.836
TOTAL (STANDARD)	1	14.77	0.24		
	2	15.17	0.22	LINEAR	<.001
	3	15.20	0.21	QUADRATIC	0.788
	4	15.52	0.19	CUBIC	0.301
FORWARD (WEIGHTED)	1	58.76	1.68		
	2	61.64	1.82	LINEAR	0.022
	3	61.82	1.77	QUADRATIC	0.291
	4	62.41	1.64	CUBIC	0.521
BACKWARD (WEIGHTED)	1	50.73	1.80		
	2	54.32	1.64	LINEAR	0.002
	3	52.74	1.60	QUADRATIC	0.994
	4	56.35	1.72	CUBIC	0.036
TOTAL (WEIGHTED)	1	109.50	3.22		
	2	115.95	2.94	LINEAR	<.001
	3	114.56	2.96	QUADRATIC	0.465
	4	118.76	2.75	CUBIC	0.053

* N=66 for all means

TABLE 26
VISUAL DIGIT SPAN

TEST	ORDER	MEAN*	S.E.	CONTRAST	P-value
LONGEST FORWARD SPAN LENGTH	1	7.55	0.17		
	2	8.00	0.15	LINEAR	<.001
	3	8.11	0.17	QUADRATIC	0.129
	4	8.26	0.17	CUBIC	0.377
LONGEST BACKWARD SPAN LENGTH	1	7.26	0.21		
	2	7.71	0.20	LINEAR	0.005
	3	7.86	0.20	QUADRATIC	0.024
	4	7.74	0.21	CUBIC	0.957
TOTAL	1	14.80	0.34		
	2	15.71	0.31	LINEAR	<.001
	3	15.97	0.32	QUADRATIC	0.007
	4	16.00	0.33	CUBIC	0.556

* N=66 for all means

TABLE 27
PATTERN MEMORY

TEST	ORDER	MEAN*	S.E.	CONTRAST	P-value
LATENCY (ALL TRIALS)	1	5.73	0.17		
	2	4.58	0.16	LINEAR	<.001
	3	4.56	0.14	QUADRATIC	<.001
	4	4.02	0.12	CUBIC	<.001
LATENCY (CORRECT TRIALS ONLY)	1	5.47	0.16		
	2	4.25	0.14	LINEAR	<.001
	3	4.33	0.14	QUADRATIC	<.001
	4	3.84	0.12	CUBIC	<.001
NUMBER CORRECT	1	23.1	0.20		
	2	22.2	0.23	LINEAR	0.108
	3	23.4	0.17	QUADRATIC	0.053
	4	23.1	0.23	CUBIC	<.001

* N=66 for all means

TABLE 28. SERIAL ORDER/PRACTICE EFFECTS (p-Values)

A. NES MAIN TESTS

TEST	MEASURE	LINEAR	QUADRATIC	CUBIC
1. Finger Tapping	Preferred Hand	NS	NS	0.014
	Nonpreferred	NS	NS	<.001
	Alternating	NS	NS	0.009
2. Visual Digit Span	Fwd Span	<.001	NS	NS
	Bwd Span	0.005	0.024	NS
	Total	<.001	0.007	NS
3. Continuous Performance Test	Reaction-time	0.024	NS	0.003
	Omissions	0.087	NS	NS
	False Positives	0.012	NS	NS
4. Symbol Digit Substitution	Correct	0.090	NS	NS
	Response Time	<.001	NS	NS
5. Serial Digit Learning Pattern Memory	Score	NS	(0.102)	NS
	Score + # trials	NS	NS	NS
	Latency (all trls)	<.001	<.001	<.001
	Latency (corr. trls)	<.001	<.001	<.001
7. Switching Attention	Side	(0.085)	NS	NS
	Direction	NS	NS	NS
	Switching	<.001	NS	NS
	Sw. Side Compat.	<.001	(0.065)	(0.097)
	Sw. Side Incomp.	0.004	NS	NS
	Sw. Dir. Compat.	<.001	NS	NS
	Sw. Dir. Incomp.	<.001	(0.072)	NS
8. Mood Scales	Tension	0.002	(0.089)	NS
	Depression	NS	NS	(0.062)
	Anger	NS	NS	NS
	Fatigue	NS	NS	0.004
	Confusion	NS	NS	0.02

Table 28 (cont.)

B. AUDITORY DIGIT SPAN TEST			
Forward (Std)	0.042	NS	(0.081)
Backward (Std)	0.002	NS	NS
Total (Std)	<.001	NS	NS
Forward (Wtd)	0.022	NS	NS
Backward (Wtd)	0.002	NS	0.036
Total (Wtd)	<.001	NS	(0.053)

C. NES SECONDARY TESTS		DIFFERENCE (ORDER 2 - ORDER 1)
1. Associate Learning	# Correct	0.022
	Recall	NS
2. Pattern Comparison	# Correct	(0.095)
	Latency (All)	<.001
	Latency (Corr. trls)	<.001
3. Simple Reaction-Time	Preferred Hand	NS
	Nonpreferred	NS
4. Syntactic Reasoning	Mean Response Time	<.001
	# Errors	<.001
	Score	0.001
5. Horizontal Arithmetic	# Correct	NS
	Response Time (All)	NS
	Response Time (Corr.)	NS

FIGURE 1
SCHEMATIC OF TEST PROTOCOL

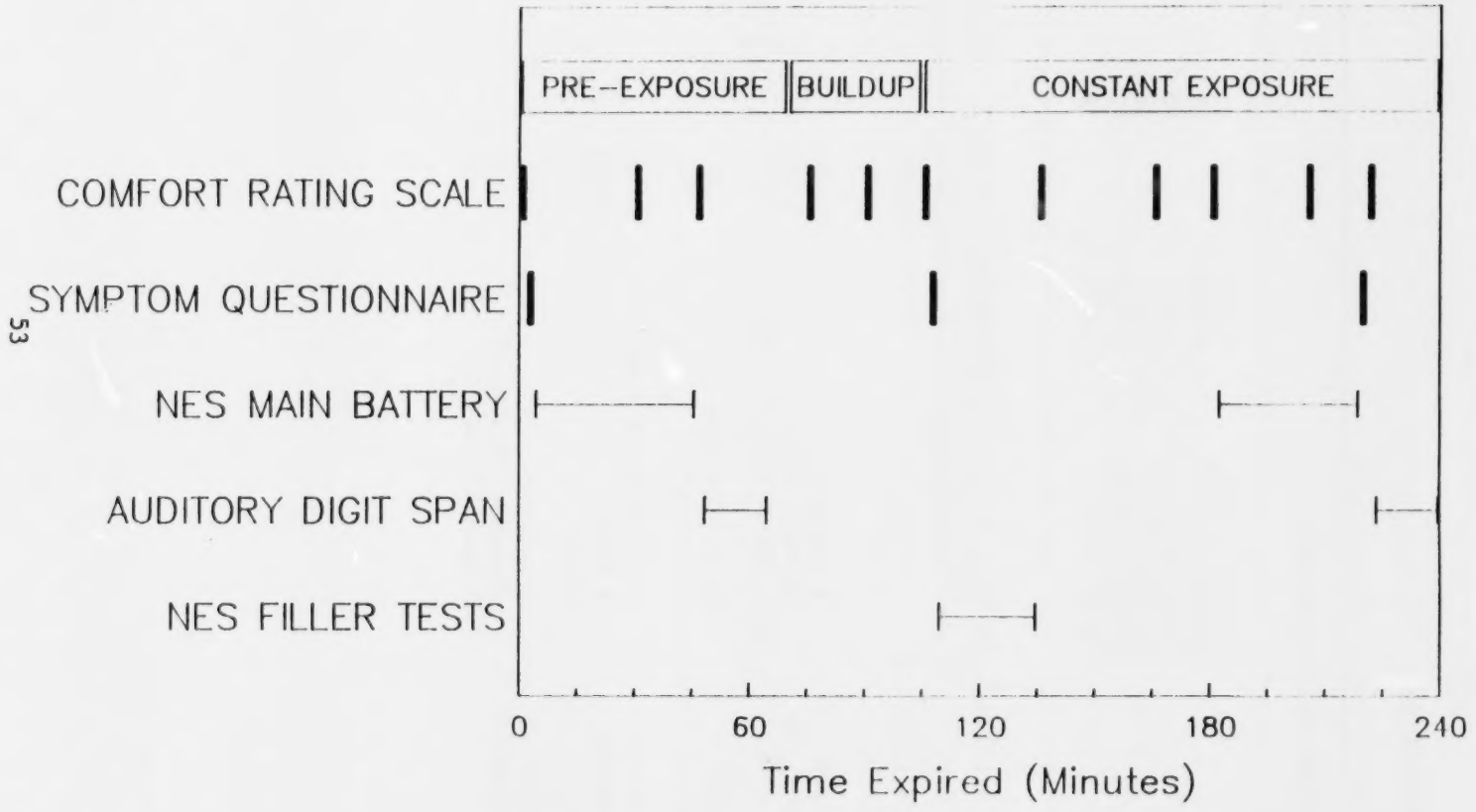


FIGURE 2
COMFORT RATING SCALE RESULTS

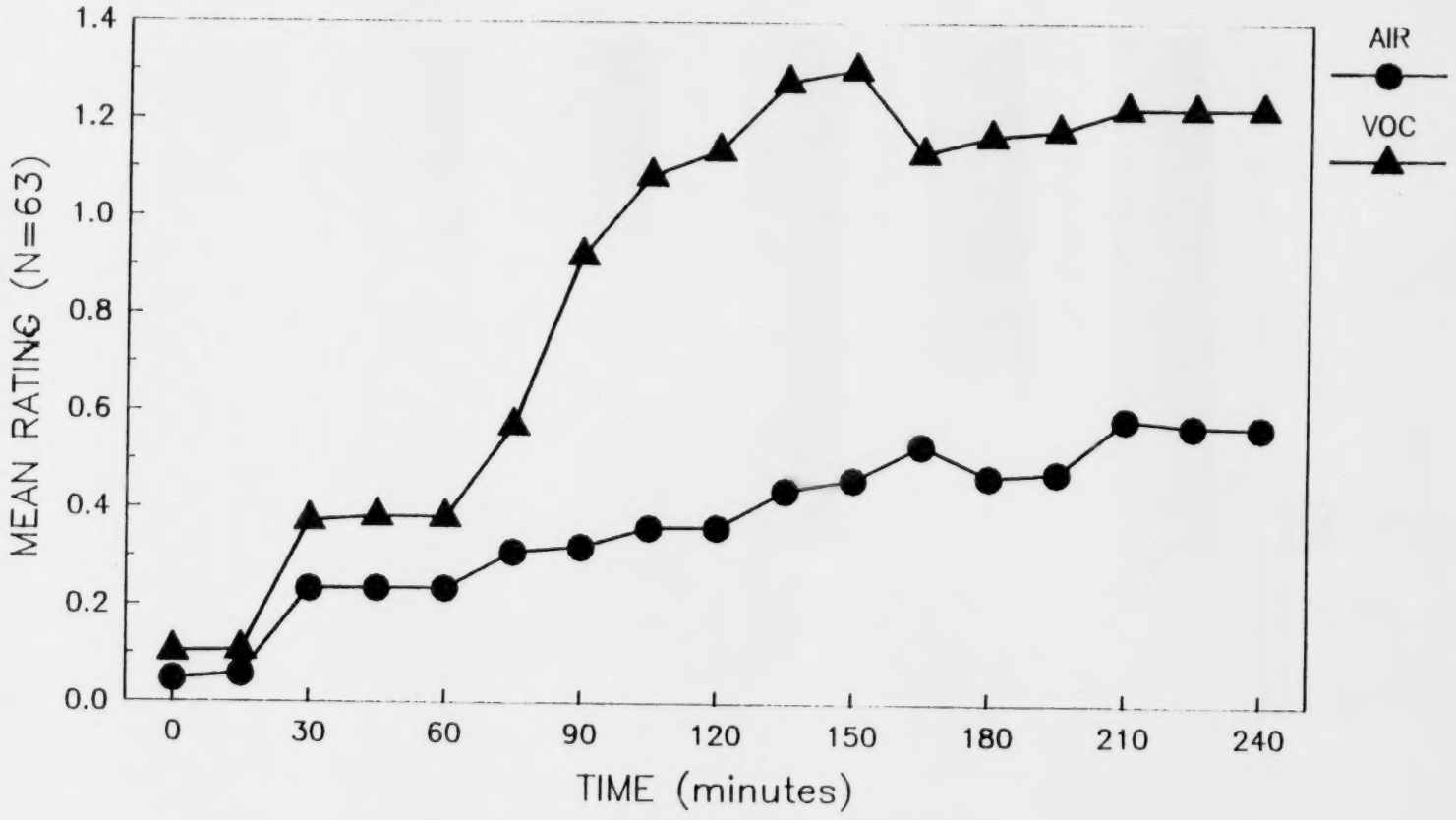


FIGURE 3
HEADACHE, ODOR & AIR QUALITY

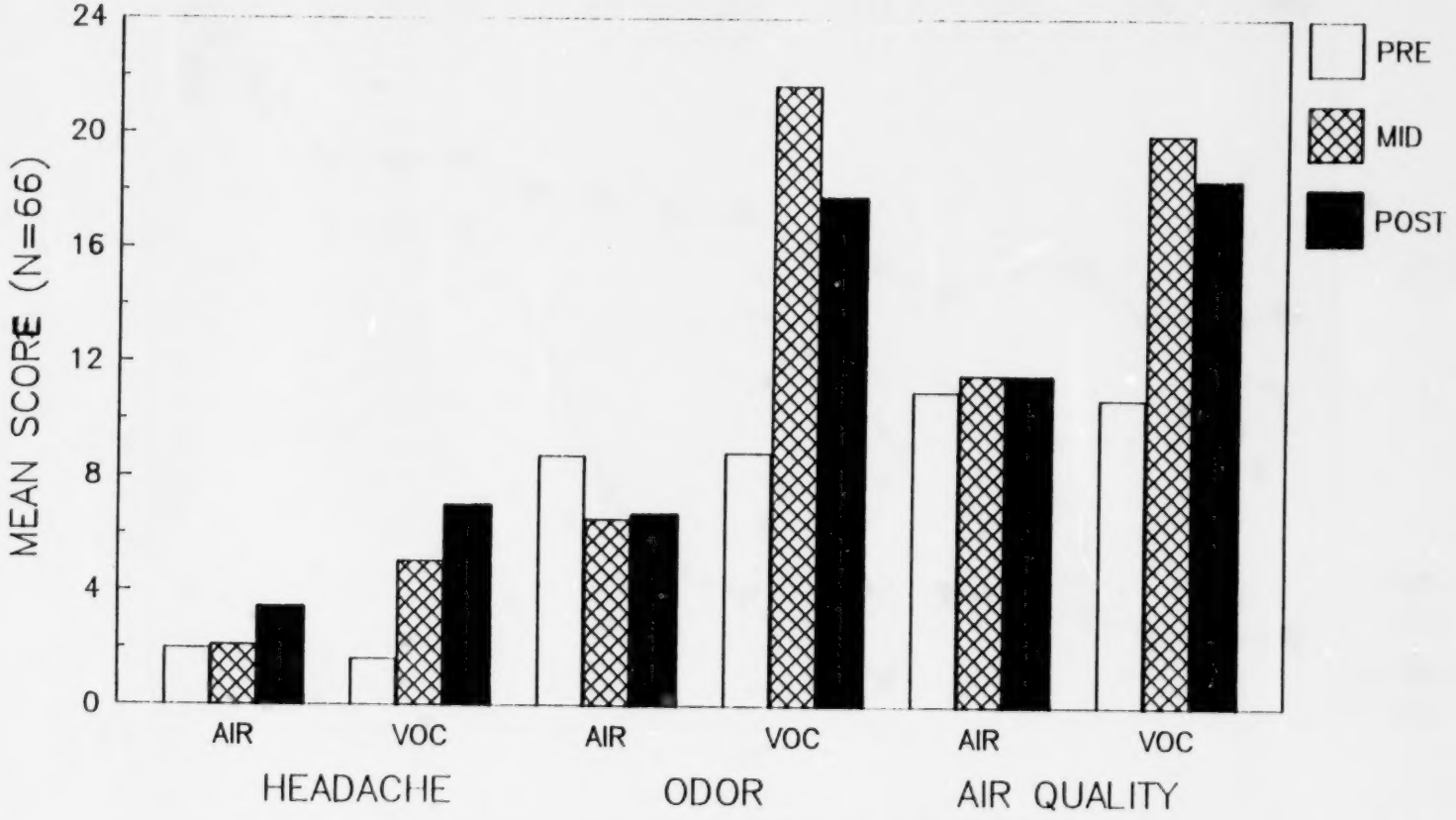


FIGURE 4
ODOR, EYE & THROAT IRRITATION

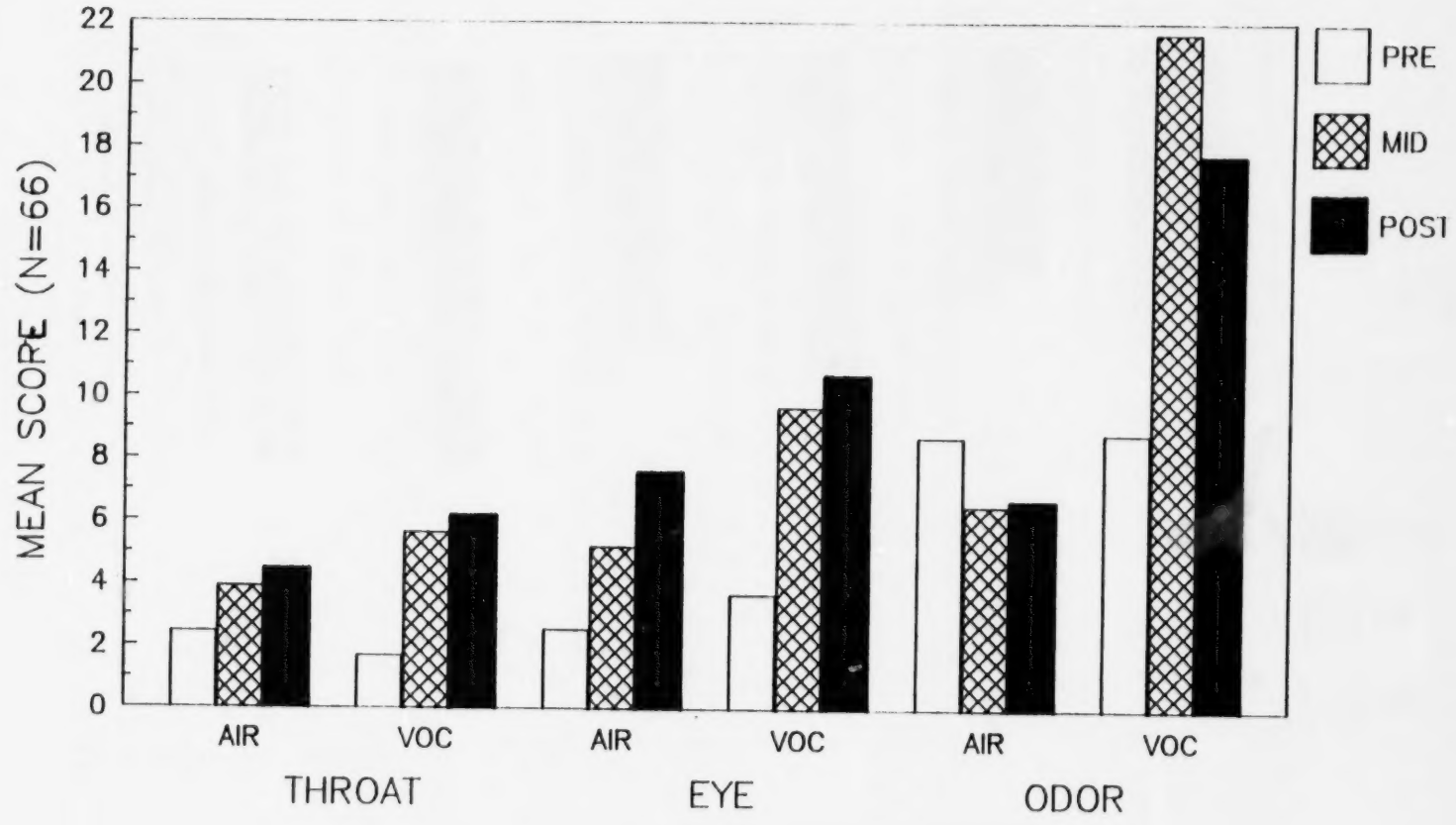


FIGURE 5
CONTROL QUESTION RESPONSES

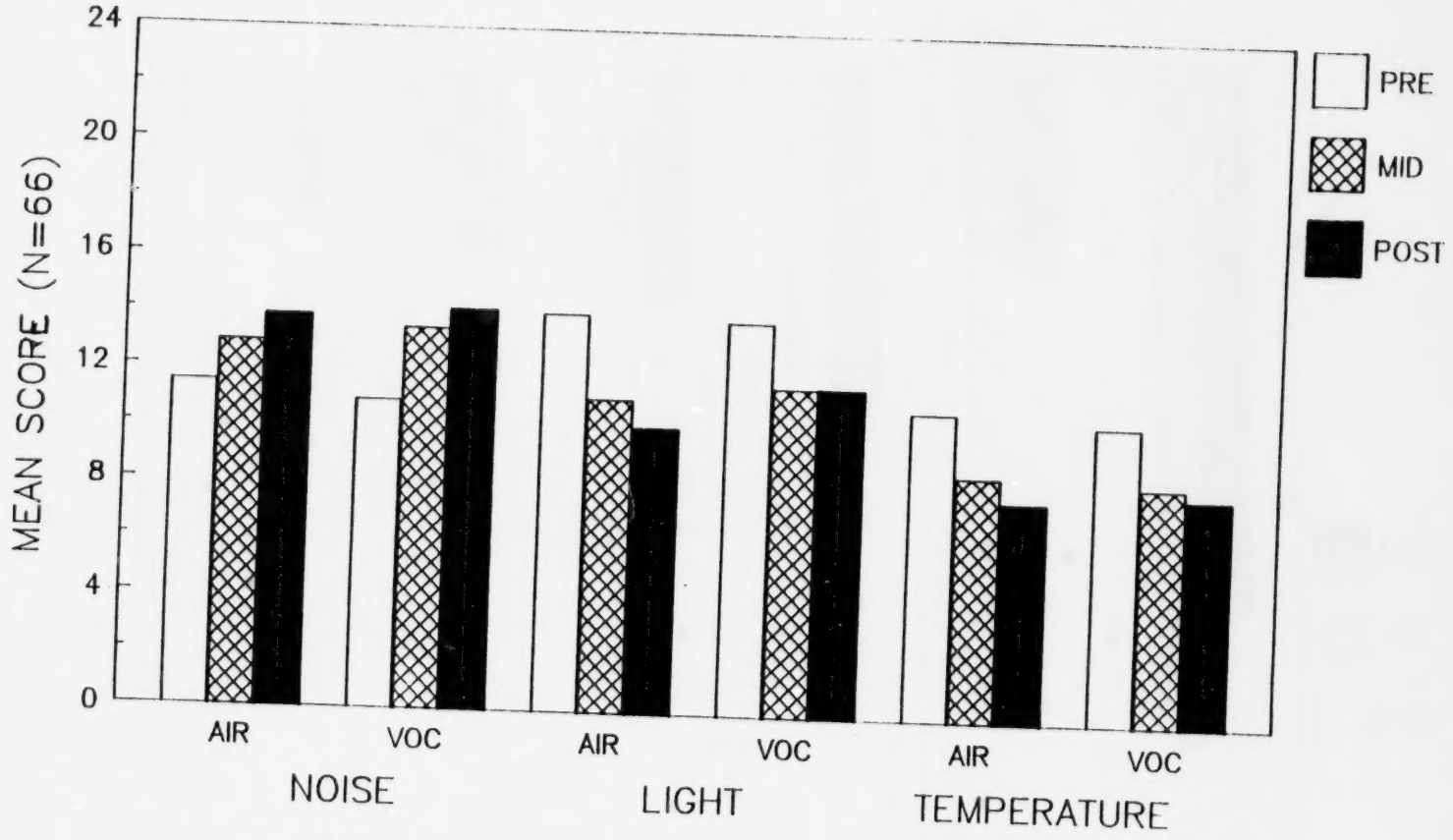


FIGURE 6
YES–NO QUESTION RESPONSES

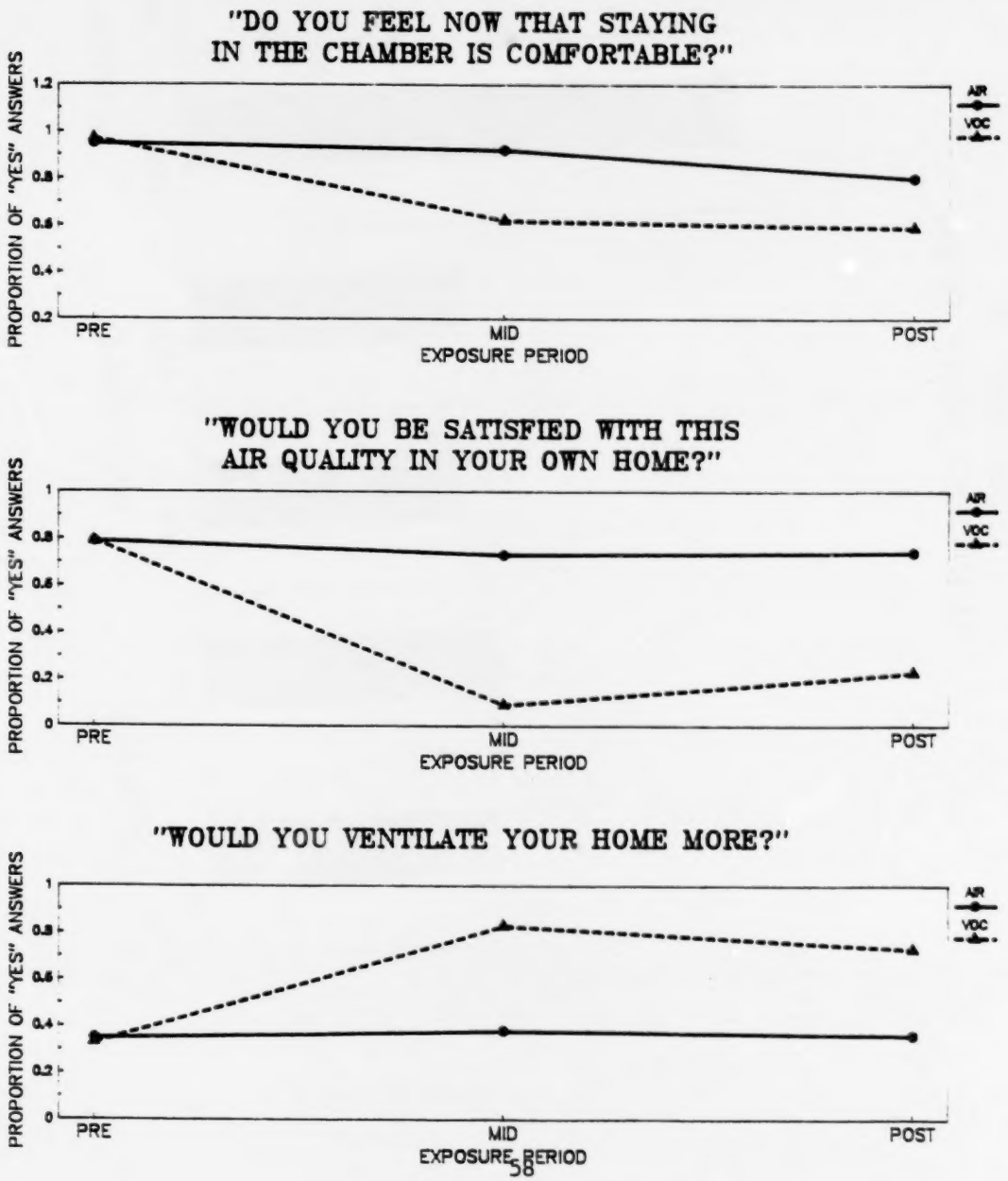


FIGURE 7
AUDITORY DIGIT SPAN

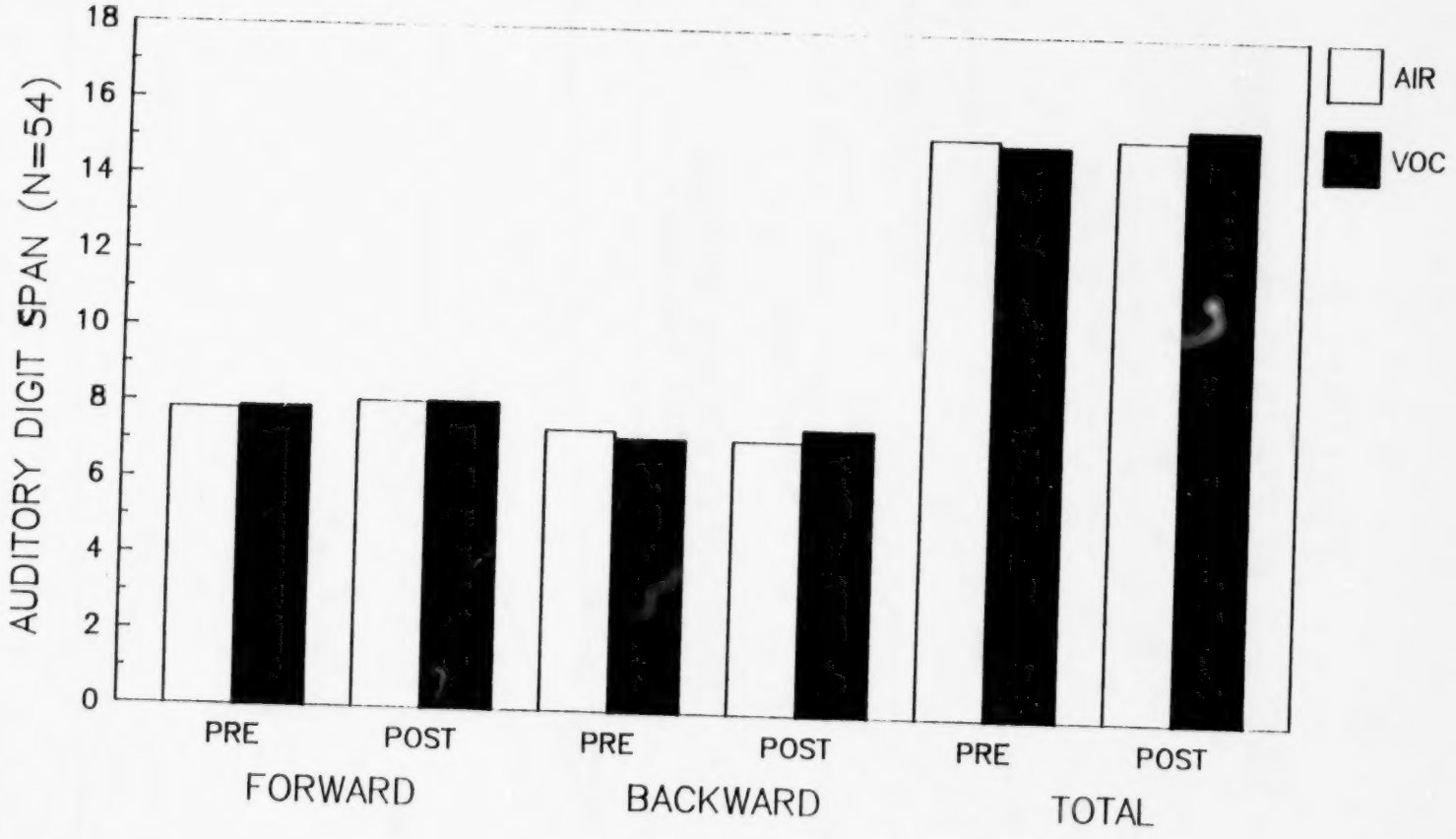


FIGURE 8
VISUAL DIGIT SPAN

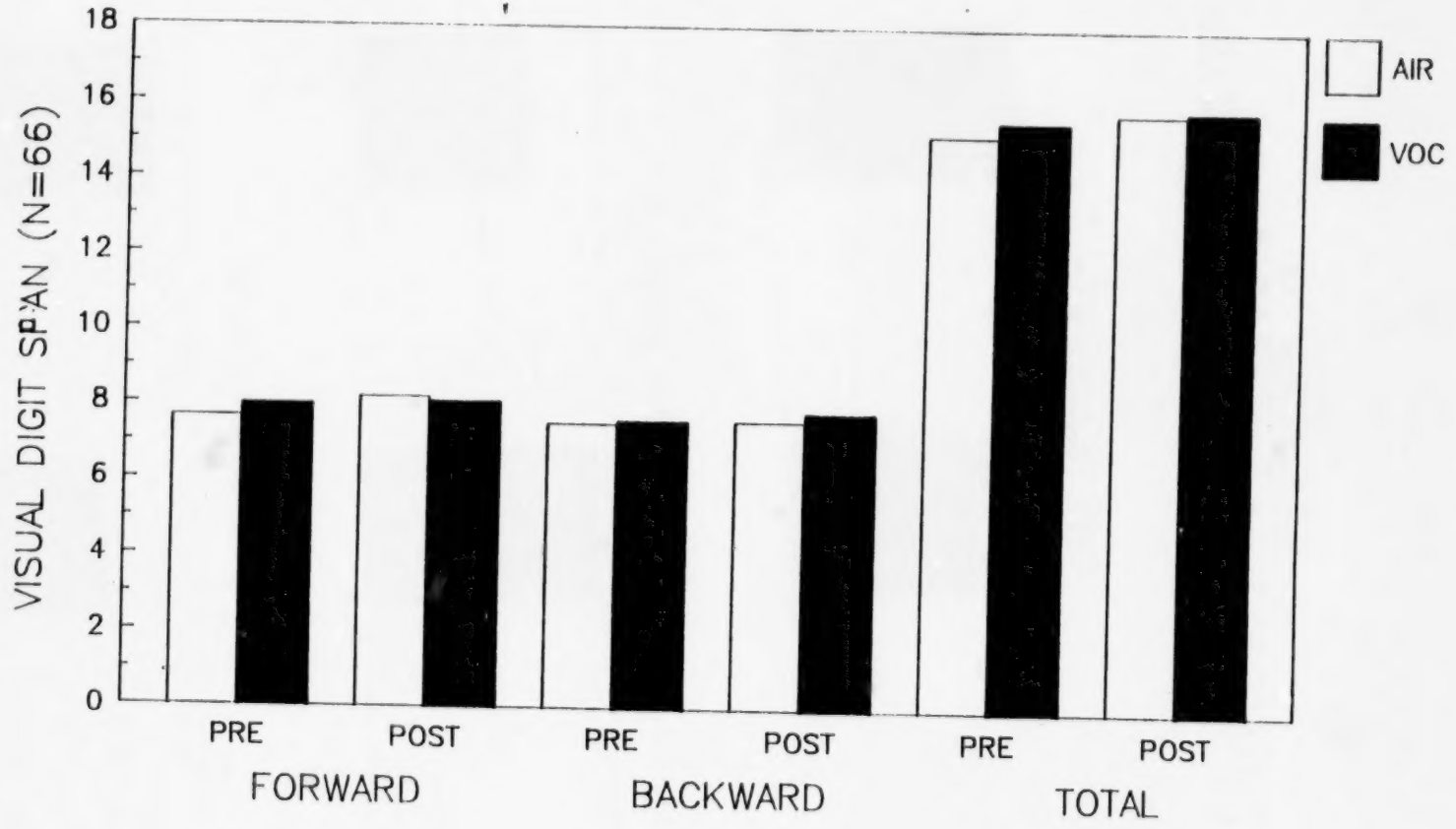
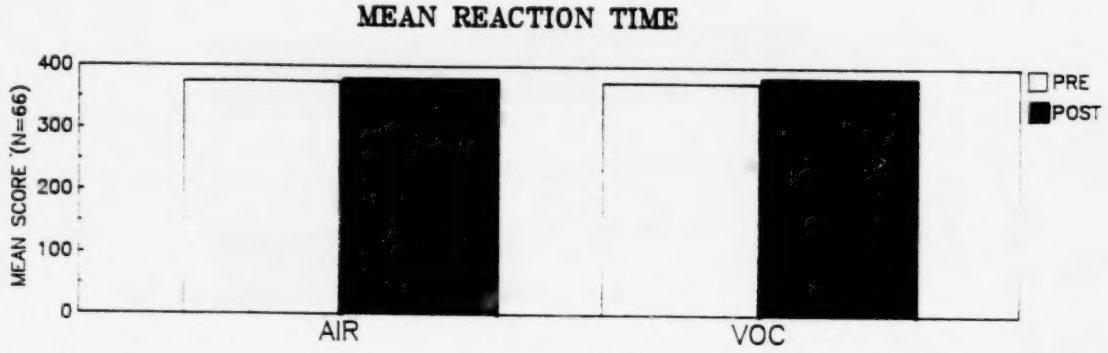
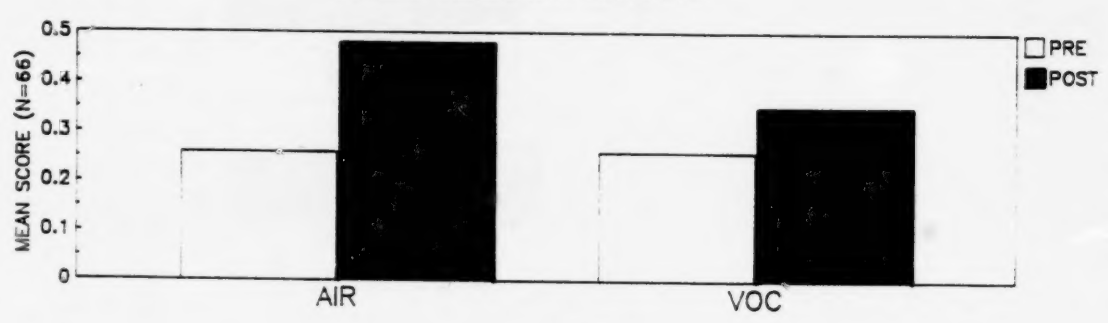


FIGURE 9
CONTINUOUS PERFORMANCE TASK





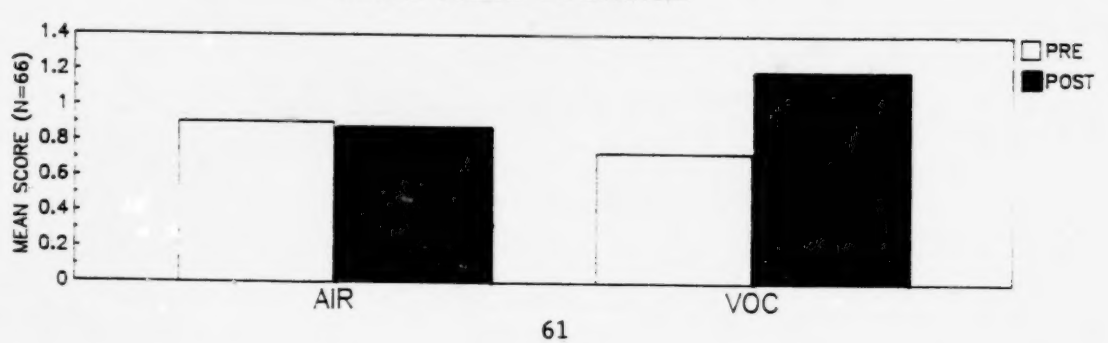


FIGURE 10

SWITCHING ATTENTION TEST

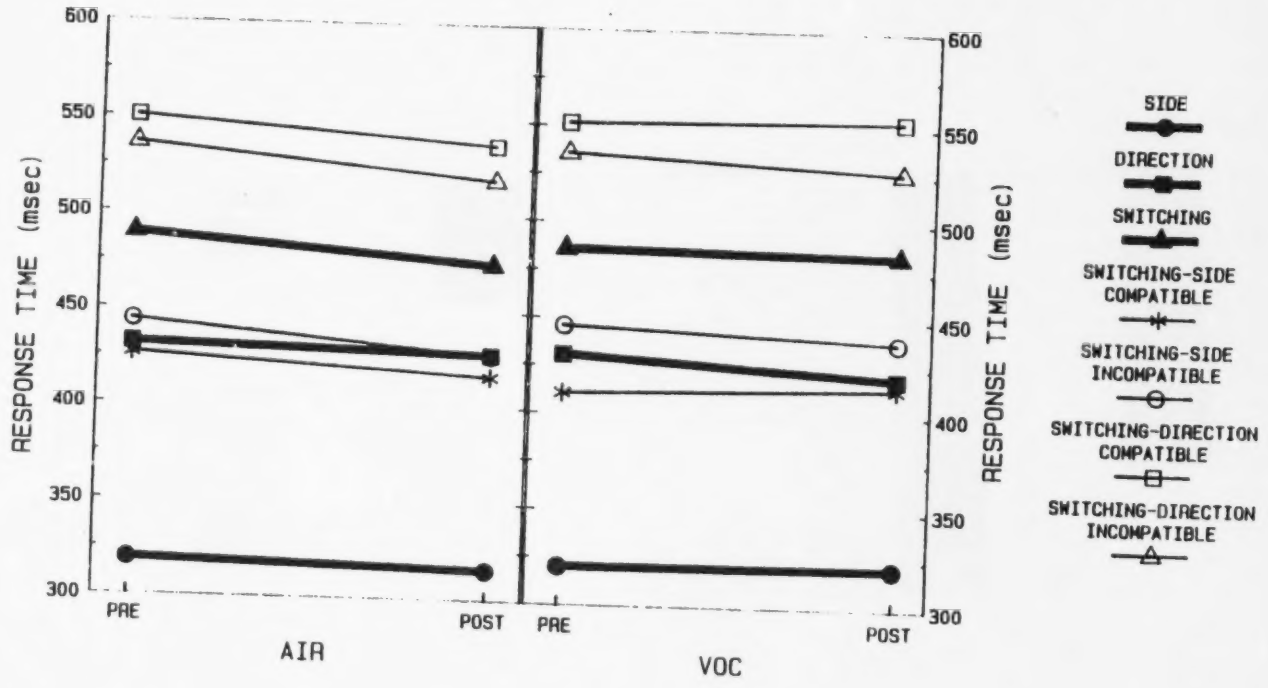


FIGURE 11

MOOD SCALE DIFFERENCE SCORES

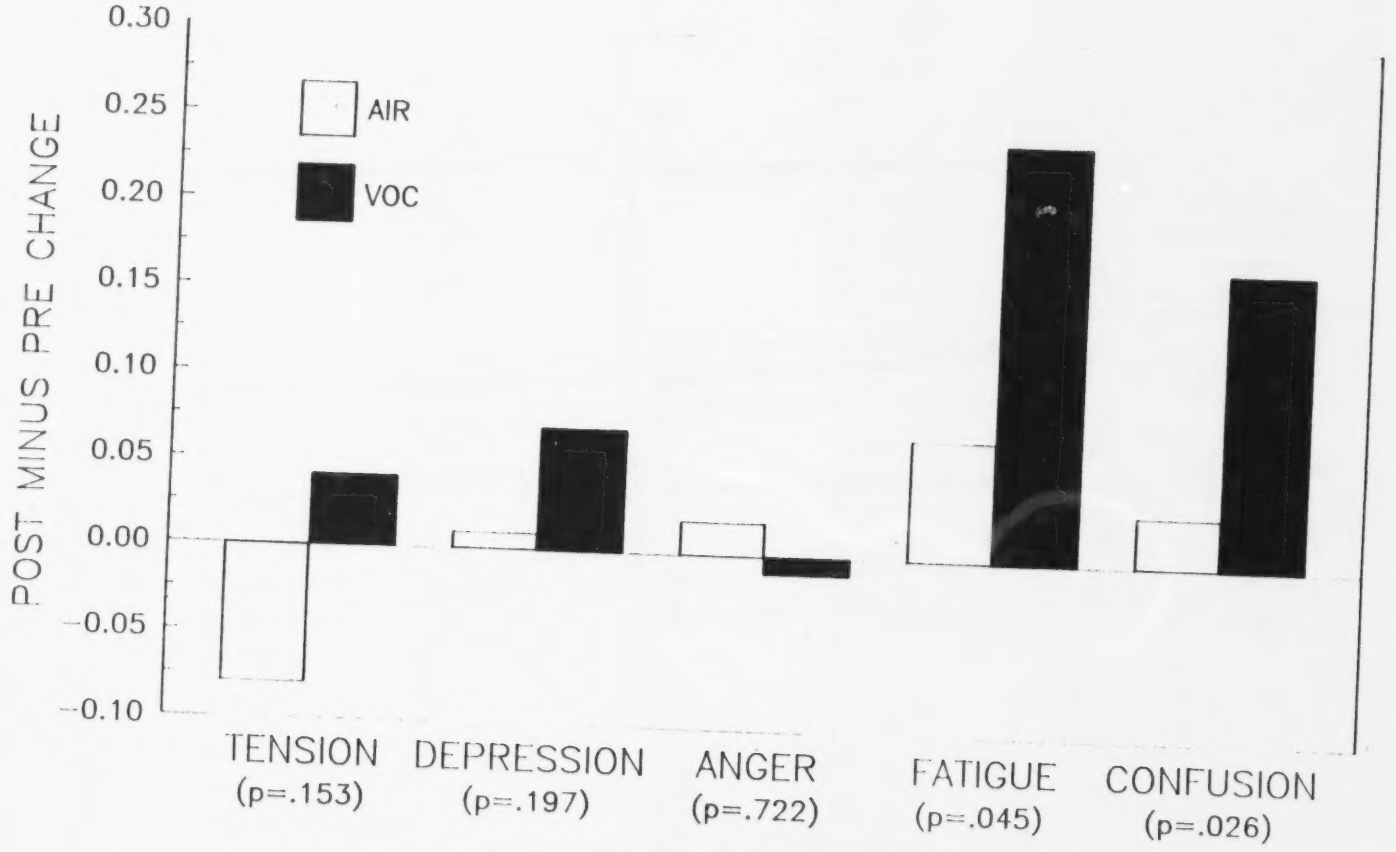


FIGURE 12

SERIAL ORDER EFFECTS
AUDITORY DIGIT SPAN

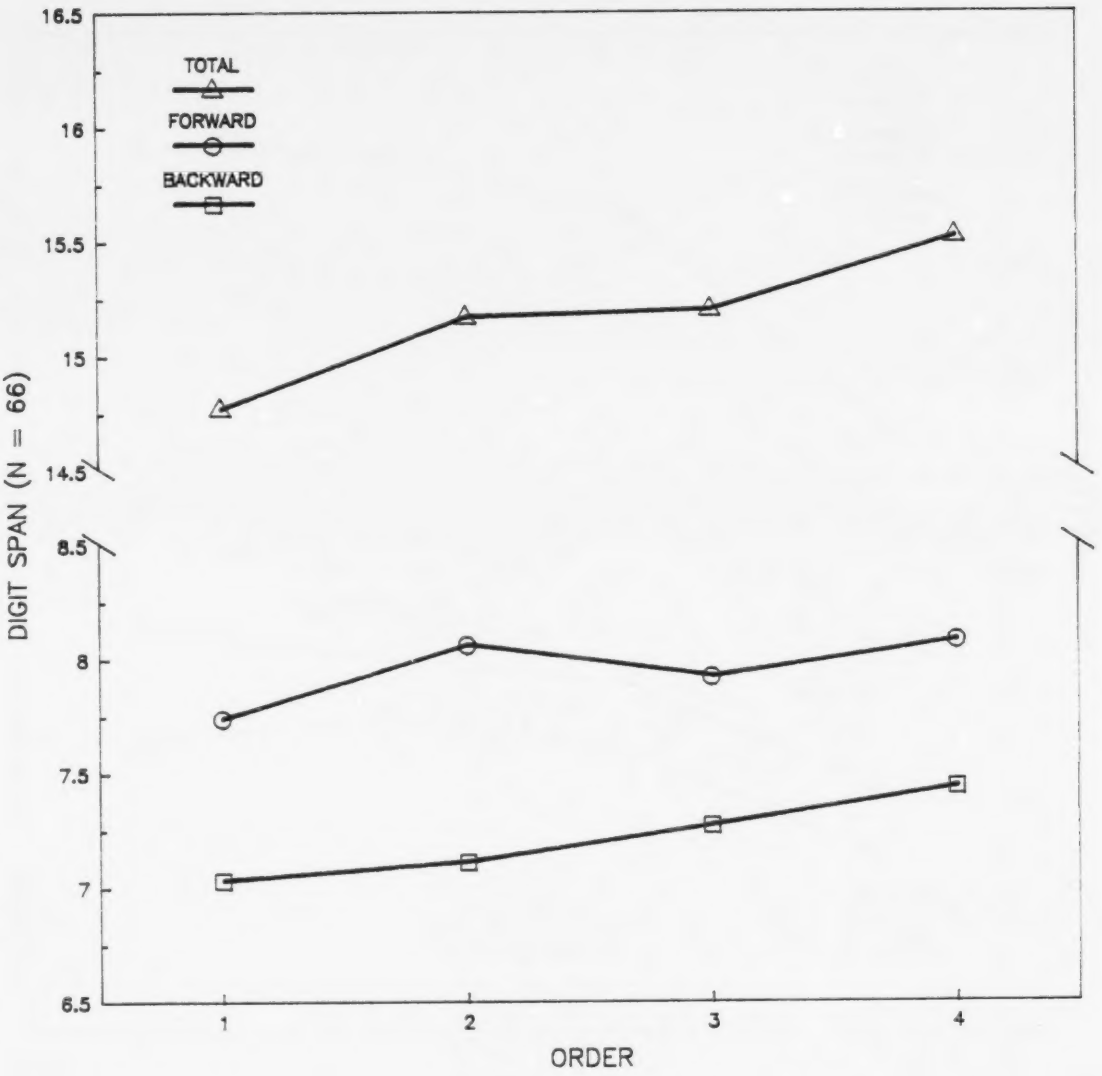


FIGURE 13

SERIAL ORDER EFFECTS

VISUAL DIGIT SPAN

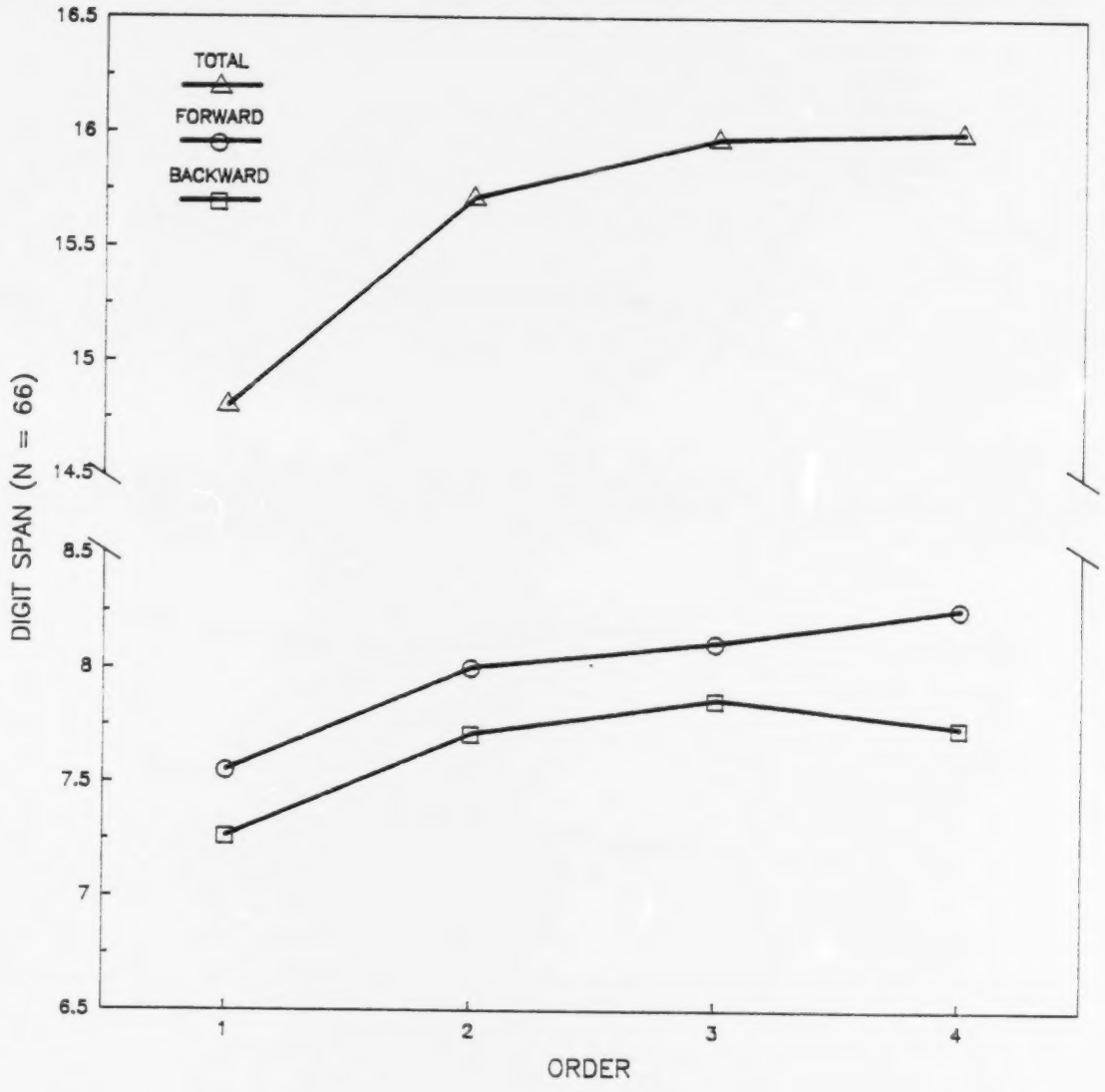


FIGURE 14
SERIAL ORDER EFFECTS
CONFUSION SCALE

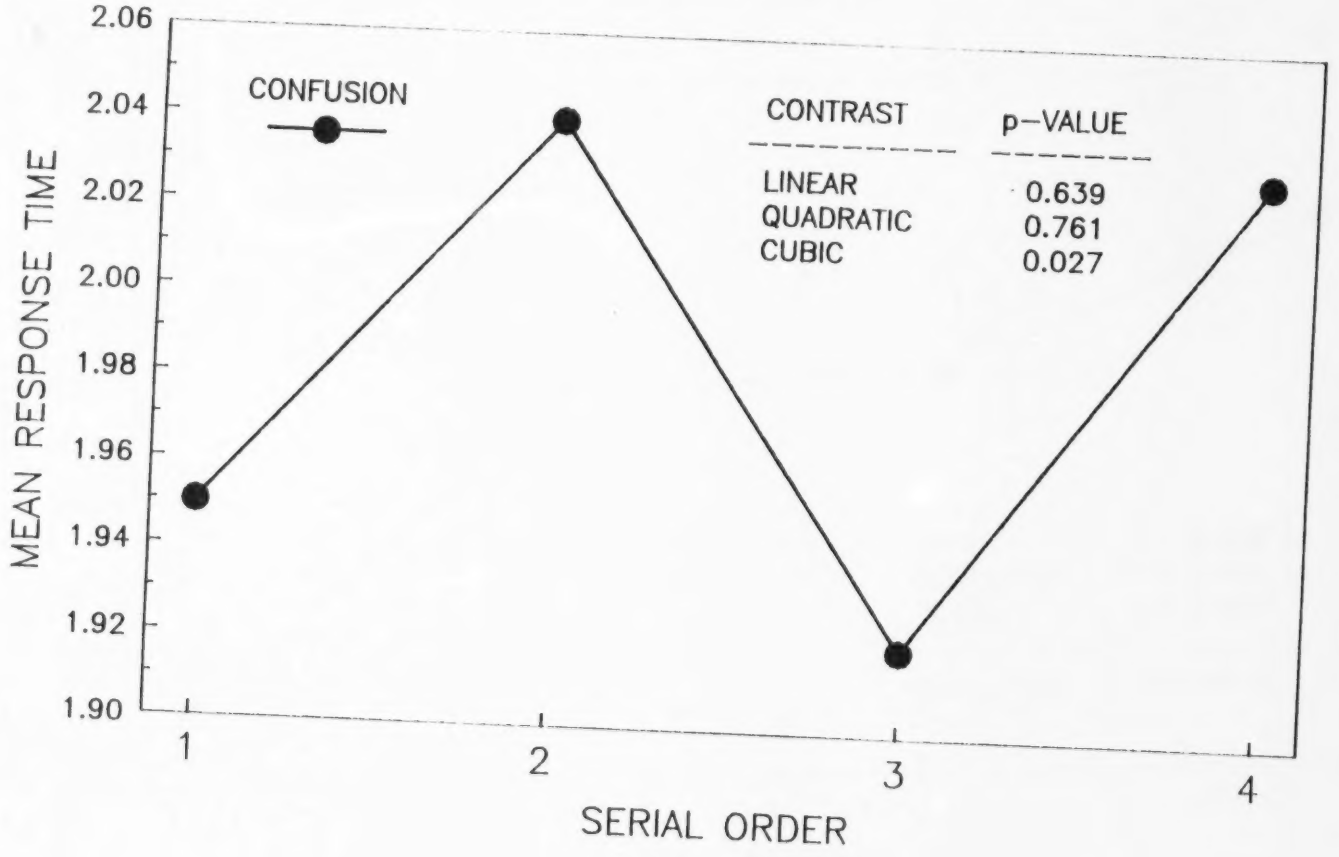
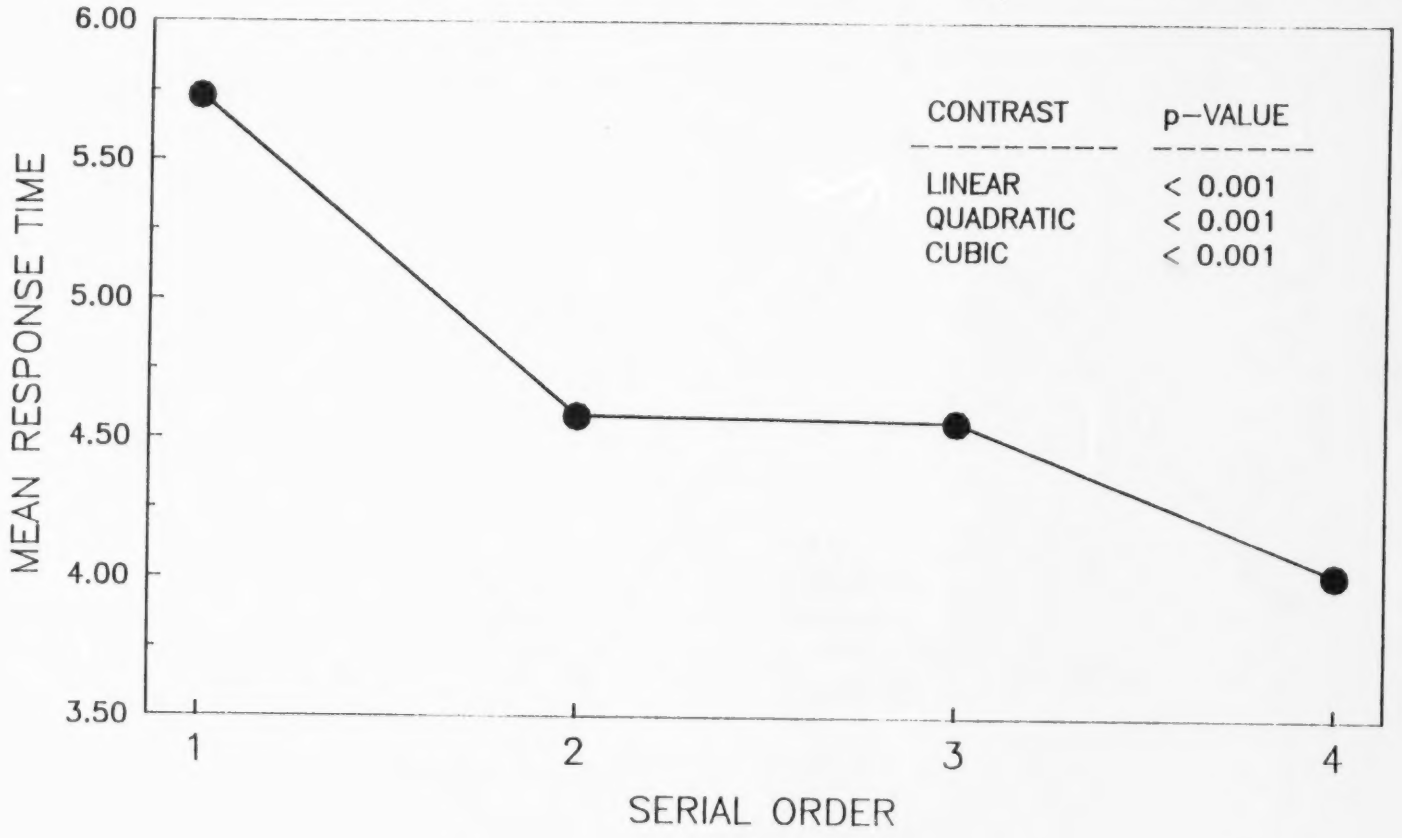


FIGURE 15
SERIAL ORDER EFFECTS
PATTERN MEMORY



APPENDIX A

DESIGN AND PERFORMANCE OF A SYSTEM TO CONTROL VOC CONCENTRATIONS WITHIN AN ENVIRONMENTAL LABORATORY USED FOR HUMAN EXPOSURE

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C-E Environmental, Inc.
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INTRODUCTION

The Environmental Protection Agency's Clinical Environmental Laboratory (CEL) on the campus of the University of North Carolina at Chapel Hill, is used to provide human exposure data which can withstand vigorous technical and legal challenge. This facility consists of of two 84 m^3 (3000 ft^3) environmental laboratories which are used to expose human volunteer subjects to constant or varying concentrations of O_3, NO_2, SO_2, CO and water soluble aerosols. The pollutant delivery system and the aerosol delivery system are under computer control. The computers are used to monitor the concentration of the pollutants, control the pollutant delivery systems, validate the data as it is taken, alarm the operator of unsafe conditions and record the data for later use. These chambers have been in continuous use since 1977 exposing subjects to pollutants and measuring responses with a computerized Physiological Data Acquisition System.

The EPA's interest in indoor air pollution and the effects of these pollutants on humans has expanded the requirements of the facility. To enable the exposure of humans to carefully controlled concentrations of Volatile Organic Compounds (VOCs), the pollutant delivery system was modified to allow injection and monitoring of the VOC compounds in one of the chambers. The following sections discuss the design and operation of the VOC generation and monitoring system.

SYSTEM DESIGN

Existing System Constraints

The VOC monitoring and delivery system was designed to be compatible with the existing pollutant control system and chambers. In contrast to other chambers, these chambers recirculate air with a flow of 3.8 m^3/sec (8000 ft^3/min) through the main loop. Fresh (make-up) air is provided at a rate of 0.56 m^3/sec (1200 ft^3/min) to replace the same amount of recirculating air exhausted through a purge damper, leaks or the chamber door when opened. The total volume of the system, chamber and associated duct work, has been calculated to be 175 m^3 (6180 ft^3) with a time constant of about 5 minutes for exchanging 67% of the chamber air. For the purpose of controlling a pollutant gas concentration, the chambers behave as a one pass chamber with a total volume of 175 m^3 and a flow rate of 0.56 m^3/sec except for the amount of pollutant needed to bring the concentration to the desired value.

Due to space constraints, the VOC generator was connected to the aerosol generator. The aerosol generator uses .38 m^3/sec (800 ft^3/min) for sweep air to dry and remove the aerosol particles from the generator. This air also moves aerosols from the generator into the main air duct where the aerosols are mixed with chamber air. This sweep air and the aerosol delivery ducts are used by the VOC generator.

The chamber design is shown in Figure 1. This figure shows recirculated air through the main chamber air loop, the fan and bypass to force air through the VOC generator, the location of the makeup air injection point and the location of the exhaust air outlet.

VOC Generator Design Considerations

The VOC generator was designed to meet a variety of stringent requirements.

The generator had to deliver precisely controlled amounts of a vaporized mixture of highly flammable VOC's to the chamber. The amount of vapor had to be automatically controlled by an existing computer and associated system. Since the mixture contains compounds with boiling points between 69 °C and 181 °C, the generator must vaporize all constituents without changing the relative concentrations of any components. The generator must also vaporize the components with a minimum of chemical reactions so that only the components in the mixture are in the chamber without generating impurities. Since VOCs are flammable, the generator must minimize the danger of explosion or fire.

The other major factor is the chamber design. Since the chamber is multipass with large internal volume and a relatively low air exchange rate, the generator uses an on-off type of control instead of proportional control. Since the design of the existing system has a 30 second control cycle, the VOC generator also incorporates this 30 second controlling period. Thus the VOC concentration can be controlled at a steady concentration by turning the solenoid valve on at the start of the 30 second period and off sometime in the middle of the period. Since the computer reports 2 minute averages, the effects of this on and off control are further minimized.

VOC Generator Design

The VOC generator (Figure 2) is a modification of a design by Molhave, which was scaled up and changed to meet increased flow requirements. The mixture of hydrocarbons is placed in an Erlemeyer flask. The top of the flask has been modified to accept a screw type fitting. This fitting allows the connection of a N_2 pressure line and a mixture delivery line. A Fairchild Model 81 precision pressure regulator is used to control the pressure over the liquid mixture. This pressure was held at 3 psig for these tests but can be varied to control the liquid feed rate. A dip tube which almost touches the bottom of the flask removes liquid from the flask. The flask is placed on a magnetic stirrer and agitated throughout the run to keep the mixture homogeneous.

The mixture delivery tube was connected through a T-connection to a Nupro

SS-SS2-KZ fine metering valve. The metering valve was fitted with Kalrez and Teflon seals. The other end of the T-connection was connected to a tube several feet long. This tube was uncapped after the mixture was pressurized to allow the mixture to fill the delivery tube. This tube was securely capped after the delivery tube was filled. The outlet of the metering valve was connected to the inlet of a Sierra Model 840V0-020 solenoid valve. The valve has a 0.02 inch orifice with Kalrez seals. The outlet of the solenoid valve was connected to the (evaporator) through a sprayer. This sprayer was constructed of two concentric tubes. The inner capillary tube alloved the mixture to enter the evaporation container. About 0.05 liters/sec (0.1 CFM) of nitrogen was passed through the outer tube. The flow of nitrogen helped spray the mixture on the bottom of the evaporation container and also forced the vapor out of the container.

The evaporator is made of glass and during operation is placed in a large brass block (15 cm in diameter and 15 cm high). The evaporator is about 8 cm in diameter and 10 cm high. A fritted glass disk separates the evaporator into two sections. The fritted glass keeps any liquid from moving from the bottom section to the top section. An arm on one side of the bottom section allows access for the sprayer. The angle of this arm allows the VOC mixture to be sprayed on the bottom of the container. Another arm, sealed at the bottom and almost touching the bottom of the container, contains a thermocouple (Omega Model C03-E) probe. The large brass block contains six 250 W cartridge heaters (McMaster-Carr P/N 3618K615) which were controlled by an Omega Model CN5001E1 proportional controller. For this mixture of compounds, the block was heated to 250 °C. After the VOC mixture has evaporated, the nitrogen forces it through the fritted glass into the top section. Here the vapor is diluted with another 0.5 liters/sec (1 CFM) of nitrogen. The flow of nitrogen was measured and controlled with an Omega Model FM064-63ST flowmeter.

The concentrated VOC vapor is then diluted with about .02 m^3/s (40 CFM) of air from the chamber. This air cools the mixture and dilutes the VOC concentration below the lower explosive limit of the compounds. A vertical 4 inch glass pipe 5 feet long allows any liquid to condense and run down the glass

into a trap. After passing through this condenser, the VOC mixture is then diluted with about .36 m^3/s (760 CFM) of the chamber air. This air is then center injected into the main air duct where it is further diluted and mixed with main recirculated air and passed through the chamber.

The use of nitrogen to dilute the VOC vapor and to force it out of the evaporator reduces the explosion and fire risk, prevents the oxidation of VOCs and minimizes the time for reactions caused by the heat required to evaporate the compounds.

VOC Monitoring and Control System

The VOC concentration in the chambers is monitored by two GowMac 23-500R total hydrocarbon analyzers. These analyzers use a flame ionization detector to monitor the hydrocarbon concentration in the chamber.

The analyzers sample from a 3 inch glass sample manifold used by all of the gaseous pollutant analyzers in the facility. This manifold draws a sample through an inverted glass funnel. The opening of this funnel is 3 meters from the floor and in the center of the chamber ceiling. The manifold exits the chamber near the ceiling of the chamber and passes over the back top of the instrument racks containing the gas analyzers. Chamber air is pushed through the sample manifold by the 0.1 inch of water positive pressure in the chamber and two sample manifold exhaust blowers. The flow though the sample manifold is 0.2 m^3/s.

Each analyzer has a tap consisting of a 1/4 inch teflon line inserted into the glass pipe so the opening is in the middle of the glass pipe. For the hydrocarbon analyzers a Mace Model 800-2334-2-0 solenoid valve is used to allow the analyzers to sample from the sample manifold or a calibration manifold. The sample is pushed into the analyzer with a Thomas Model 107CA14TFEL pump with teflon coated piston, valves and cylinder.

A PDP 11/35 computer measures the output of each analyzer once per second. These samples are used to generate 2 minute averages which are reported to

investigators as the chamber concentration. For control purposes, the computer samples the concentration in the chamber every 30 seconds and determines the percent on time for the VOC valve accordingly. This value is converted to a voltage and sent to the VOC control card. Depending on the state of the system, this card uses a voltage from a potentiometer in the manual mode or the voltage from the computer in the automatic mode, to control the duty cycle of the valve. This allows either automatic or manual control of the generator. In the automatic mode, another signal from the computer forces the card to synchronize with the computer.

System Calibration The VOC concentration in the Molhave study was 25 mg/m^3 toluene equivalent. Molhave calibrated FID analyzers with toluene and controlled the VOC concentration with instrument output at the same level obtained with the toluene calibration standard. The 25 mg/m^3 was converted to 7 ppm toluene equivalent for these studies. The VOC analyzers were calibrated with toluene and the concentrations reported in terms of toluene. A standard of toluene diluted with nitrogen was diluted to the various concentrations with ultra high purity zero air with the dilution calibration system which has been used for 12 years. This system is automatically controlled by the computer which after the calibration has been specified by the operator, automatically calibrates the analyzers. The standard calibration consisted of three span points (5, 7 and 9 ppm) and a zero point. The zero was taken first, then the highest point was taken twice with the first one thrown out.

System Operation The following procedure was used to run a session of the protocol.

1. The instruments were calibrated the morning of the protocol using the method given above.

2. A new solution was mixed up. Several safeguards were followed to assure that the mixture was made correctly. The operator used a check sheet to remove a bottle of each of the chemicals from a storage cabinet. Each chemical was pipetted using its own premarked pipette

(both with chemical name and the volumne) from the bottle to the flask. As this was done, the chemical was checked off on the check sheet. The bottle was then placed back in storage.

3. After the mixture was prepared, it was connected to the system.

4. The generation system was turned on and heated to the proper temperature during instrument calibration and chemical mixing.

5. The results of the calibration were then checked and the new calibration constants loaded into the computer.

6. The computer was instructed to monitor the VOC concentration in the chamber.

7. Just before VOC generation was initiated, the ambient chamber VOC concentration was measured and the exposure level (7 ppm) was incremented by the ambient VOC level. For example, if the ambient VOC level was 0.37 ppm, the exposure level was set at 7.37 ppm.

8. Seventy-five minutes after commencement of testing, the operator initiated exposure by activating the automatic control of the VOC concentration in the chamber.

SYSTEM PERFORMANCE

This system has been used in two different studies for a total of 110 hours of VOC control during a protocol. The two studies used a mixture very similar to the twenty-two compounds Molhave used. Figure 3 shows a plot of the VOC concentration in the chamber over the period of the protocol. For this study, the subjects were in the chamber while the VOC control was established and the system equilibrated to the required valve.

1

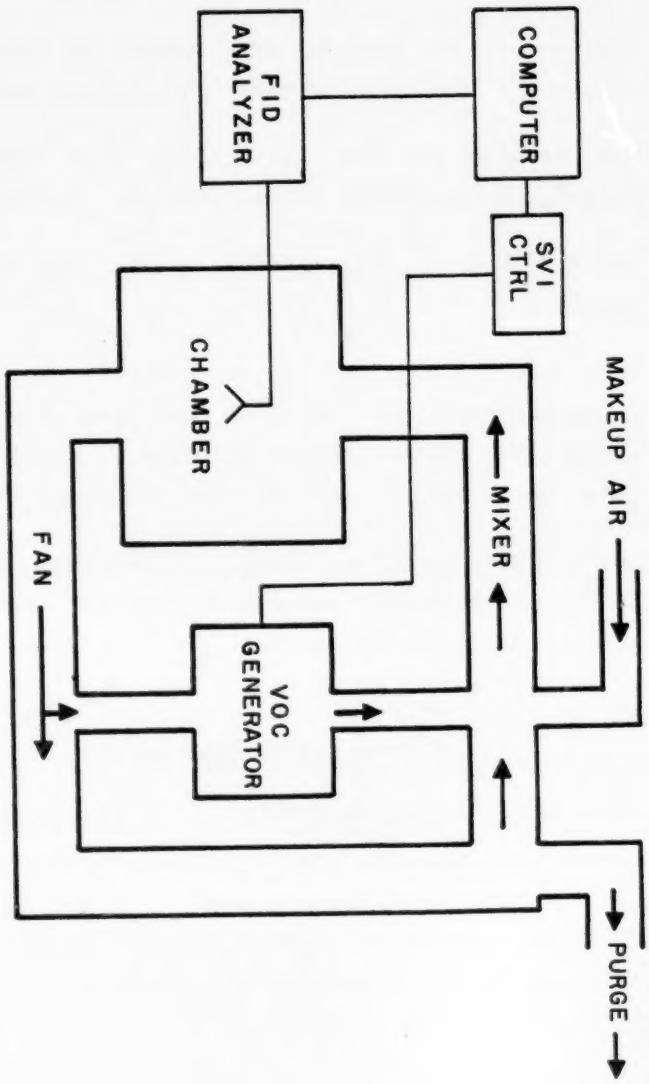


Figure 1
Overall Chamber Design

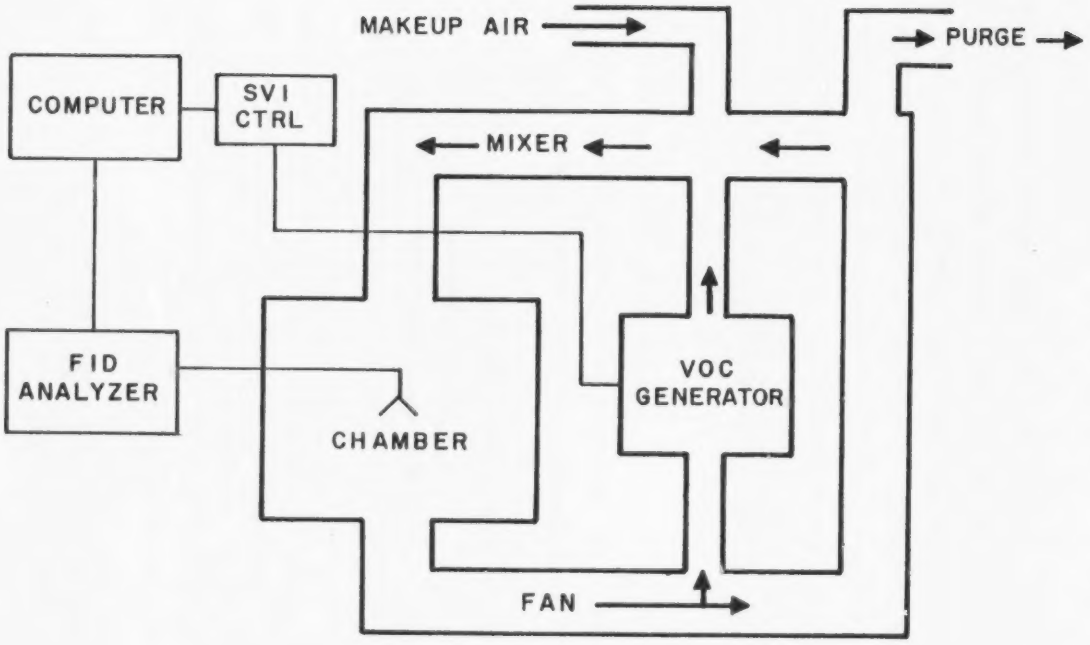
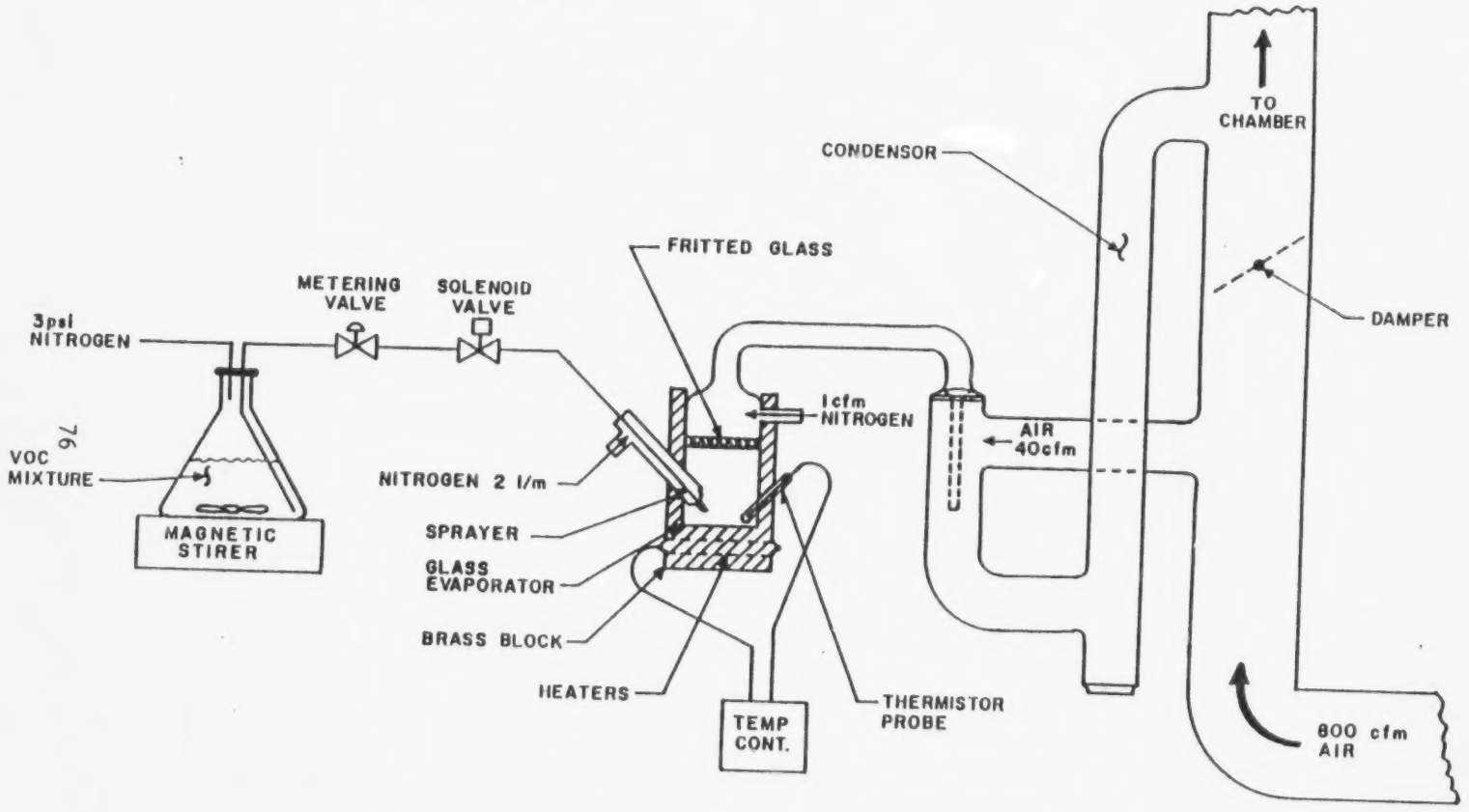


Figure 1
Overall Chamber Design

Figure 2

VOC Generator Design



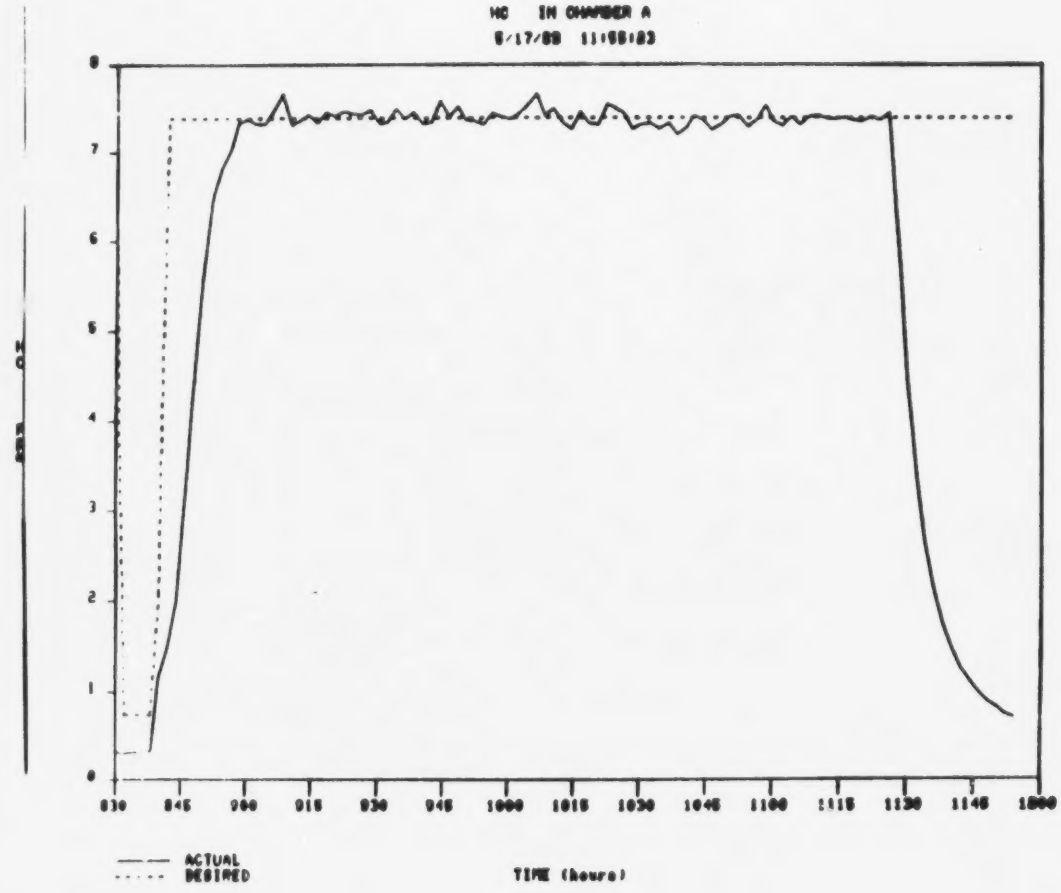


Figure 3
Typical Plot of VOC Control

REFERENCES

Molhave L, Bach B and Pedersen O. Klimakammerundersogelse af geneforekomster hos personer, der udsaettes for organiske gasser og dampe fra byggematerialer [Human reactions to volatile organis gases]. Project Report R00-52(22411), Institute of Hygiene, Universitetsparken, Aarhus, Denmark, 1985.

Strong AA; "Description of the CLEANS Human Exposure System". U.S. EPA. EPA-600/1-78-064, 1978.

Crider WL, Landis DA, Weaver FH. In "Generation of Aerosolos and Facilities for Exposure Experiments". Willeke K, (ed.) Ann Arbor, Michigan, 1980:493-515.

Glover DE, Berntsen JH, Crider, WL, Strong AA. "Design and Performance of a System to Control Concentrations of Common Gaseous Air Pollutants within Environmental Laboratories Used for Human Exposure". J. Environ. Sci. Health, A16(5), 1981, pp501-522.

APPENDIX B

AUDITORY DIGIT SPAN TEST DESCRIPTION AND INSTRUCTIONS

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The following tape-recorded instructions were given to subjects. "Attention Subjects: you will now be given another version of the digit span test. Unlike the Digit Span Test you took earlier on the computer, this test will be administered by a cassette recording played over your speakers. Please write your responses on the answer sheet attached to the clipboard. Please pick up the clipboard at this time and assume a comfortable writing position.

The answer sheet should say "auditory digit span - pretest" at the top. The test will have two parts, Digit Forward and Digit Backward. Please find the section labeled Digit Forward. As you can see on the answer sheet, blank spaces are provided for you to write down each of the digits in the string. The first string will contain 3 digits. Please listen carefully as the digits are called out. Be sure not to repeat the digits verbally, but you may rehearse them in your mind. After the string has been called out, there will be a pause during which you are to write down the digits as you remember them and in the same order as they were presented. Please do not begin writing until all digits in the string have been called out. After the pause, a different string of 3 digits will be presented and then followed by a pause during which you can write your answers. This process will be repeated until 2 trials with strings of up to 9 digits have been presented.

After the digit forward test has been completed there will be a 1 min. pause. Then, the digit backwards test will begin. This test is exactly like the digit forward test except that you are to write down the digits in the reverse order of their presentation. That is, the last digit you hear should be

the first digit you write on the answer line. The digit backwards test will begin with a 2 digit string and end with an 8 digit string. Please remember, do not repeat the digits out loud and do not begin to write your answers until the pause begins after all the digits in the string have been called out. Please prepare to begin the digit forward test. Write the digits in the same order as they are presented. The test will begin now.

Trial	1	of	3	digits	(say	1-4-7	and	pause	10	sec.)
Trial	2	of	3	digits	(say	3-7-2	and	pause	10	sec.)
"	1	"	4	"	(	" 2-9-5-6	and	"	12	sec.)
"	2	"	4	"	(	" 2-6-5-4	and	"	12	")
"	1	"	5	"	(	" 2-8-7-4-5	and	"	14	")
"	2	"	5	"	(	" 2-9-6-7-5	and	"	14	")
"	1	"	6	"	(	" 1-6-9-2-4-1	and	"	16	")
"	2	"	6	"	(	" 4-7-6-1-2-8	and	"	16	")
"	1	"	7	"	(	" 5-7-1-6-2-4-9	and	"	18	")
"	2	"	7	"	(	" 1-5-2-8-9-4-6	and	"	18	")
"	1	"	8	"	(	" 7-3-9-8-4-5-2-7	and	"	20	")
"	2	"	8	"	(	" 8-7-4-2-5-4-3-1	and	"	20	")
"	1	"	9	"	(	" 3-7-4-9-7-3-8-4-2	and	"	22	")
"	2	"	9	"	(	" 1-3-2-5-2-7-8-4-8	and	"	22	")

The digit forward test is now completed. We will pause for 1 min. before beginning the digit backwards test. (pause 1 min.) Please prepare to begin the digit backwards test. Please write the digits in the order opposite that in which they are presented. The test will begin now".

Trial	1	of	2	digits	(say	3-5	and	pause	10	sec.)
Trial	2	of	2	digits	(say	4-2	and	pause	10	sec.)
"	1	"	3	"	(	" 2-9-2	and	"	12	")
"	2	"	3	"	(	" 3-2-5	and	"	12	")
"	1	"	4	"	(	" 2-7-9-4	and	"	14	")
"	2	"	4	"	(	" 2-8-9-4	and	"	14	")
"	1	"	5	"	(	" 3-6-7-5-1	and	"	16	")
"	2	"	5	"	(	" 2-6-9-7-3	and	"	16	")
"	1	"	6	"	(	" 1-4-8-3-9-3	and	"	18	")
"	2	"	6	"	(	" 7-3-6-2-4-1	and	"	18	")
"	1	"	7	"	(	" 4-1-6-7-9-5-1	and	"	20	")
"	2	"	7	"	(	" 2-9-6-7-2-1-4	and	"	20	")
"	1	"	8	"	(	" 1-4-2-6-7-5-6-9	and	"	22	")
"	2	"	8	"	(	" 1-6-1-3-9-8-3-7	and	"	22	")

Similar instructions were given for the post test. Digits presented in the post test were:

FORWARD
2-8-6
3-2-6
1-5-7-3
9-3-5-1
6-8-1-9-2
8-2-5-7-3
2-8-6-1-3-7
2-4-8-7-5-1
9-5-1-3-1-7-2
6-3-5-7-2-8-5
1-5-9-5-7-3-9-2
1-6-9-3-4-8-6-2
2-8-1-5-2-6-1-7-3
4-1-4-8-2-6-9-4-1

BACKWARD
1-4
2-8
5-2-7
1-3-8
3-7-9-5
6-1-4-7
2-8-9-5-6
2-9-5-2-1
1-3-4-8-2-1
5-9-3-8-7-2
4-5-7-4-1-6-7
3-9-5-9-1-5-7
1-7-4-3-2-9-1-6
9-4-8-2-7-1-3-2

Digit Sequences used on day 2 were as follows:

FORWARD PRE-TEST
1-4-2
6-1-3
3-5-1-7
8-9-4-2
5-9-8-1-6
2-8-9-4-6
3-1-4-2-4-7
3-7-9-2-6-1
2-9-3-7-9-4-6
8-5-1-7-2-4-3
7-1-4-6-8-3-2-9
9-4-7-3-2-9-5-6
1-6-2-5-1-8-2-7-3
7-3-9-3-8-4-5-7-2

BACKWARD PRE-TEST
1-5
2-6
1-4-2
1-8-7
5-2-4-1
2-4-6-5
3-1-5-4-6
6-3-5-1-7
2-9-1-3-8-4
3-6-7-5-2-8
7-3-7-1-8-1-4
6-1-3-7-9-8-2
2-9-4-7-5-1-4-9
4-2-4-1-7-3-6-8

POST TEST-FORWARD
7-4-1
2-8-9
1-6-8-7
5-2-7-1
2-7-3-1-4
1-5-8-3-9
9-3-4-7-6-1
4-6-2-8-1-3
3-7-8-9-1-3-5
3-2-4-5-7-9-6
2-7-8-6-9-3-4-8
9-4-3-5-8-2-1-5
8-3-7-4-6-9-2-3-1
5-2-3-1-4-9-2-6-8

POST TEST-BACKWARD
3-9
3-1
2-9-5
2-6-9
1-4-5-8
3-2-8-6
7-3-2-4-1
5-6-1-4-3
7-3-5-1-2-6
8-5-2-7-3-1
3-2-3-5-4-2-1
4-3-6-5-7-8-2
1-5-3-9-4-8-2-6
1-6-9-3-8-2-7-1

Digit Span Answer Sheet

Subject ID Number : _____ Session # (Circle one): 1 4 7

Date : _____ Day (Circle one) : 0 1 2

A. Digit Forward

3. (1) _ _ _
   (2) _ _ _

4. (1) _ _ _ _
   (2) _ _ _ _

5. (1) _ _ _ _ _
   (2) _ _ _ _ _

6. (1) _ _ _ _ _ _
   (2) _ _ _ _ _ _

7. (1) _ _ _ _ _ _ _
   (2) _ _ _ _ _ _ _

8. (1) _ _ _ _ _ _ _ _
   (2) _ _ _ _ _ _ _ _

9. (1) _ _ _ _ _ _ _ _ _
   (2) _ _ _ _ _ _ _ _ _

B. Digit Backward

2. (1) _ _
   (2) _ _

3. (1) _ _ _
   (2) _ _ _

4. (1) _ _ _ _
   (2) _ _ _ _

5. (1) _ _ _ _ _
   (2) _ _ _ _ _

6. (1) _ _ _ _ _ _
   (2) _ _ _ _ _ _

7. (1) _ _ _ _ _ _ _
   (2) _ _ _ _ _ _ _

8. (1) _ _ _ _ _ _ _ _
   (2) _ _ _ _ _ _ _ _

INSTRUCTIONS FOR SCORING AUDITORY DIGIT SPAN DATA

ADS data will be scored in two ways, the standard method (std) and the weighted method (wtd).

Procedure.

Both Methods. Start with the 3 digit forward string, trial 1. Use the answer key to see if all 3 digits are correctly recorded on the answer sheet. If so, put a checkmark at the right end of the string. If no, put an X at the right end. Repeat this process for each string in the digit forward test. Then score the digit backward test.

Std Method. At the bottom of the answer sheet under the forward responses, write the number of the string that corresponds to the longest string in which at least 1 of the 2 trials was answered correctly for that string and all previous strings. For example, if at least 1 trial is correctly answered on strings 3, 4, 5 and 6 but neither trial is answered correctly on the string of 7 digit, the score is "std = 6". Repeat this procedure for the digit backwards test. At the center, record the total score. For example, if the forward score is 6 and the backwards score is 5, write "Tstd = 11".

Wtd Method. For the digit forward test, multiply each string number (3-9) by the number of trials answered correctly (0,1 or 2). Add all products together. For example, if the scores are:

string	# trials correct	the products are
3	2	3 x 2 = 6
4	2	4 x 2 = 8
5	2	5 x 2 = 10
6	1	6 x 1 = 6
7	0	7 x 0 = 0
8	1	8 x 1 = 8
9	0	9 x 0 = 0

The product sum = 38. Write "Wtd = 31" under the forward responses. Repeat this procedure for the backwards test. Record the total Wtd score at the bottom of the answer sheet in the center. For example, if the forward score is 38 and the backwards score is 26, write "Twtd = 64".

Note. For the backwards test, remember that the answer must be in the reverse order of presentation to be correct.

APPENDIX C

NEUROTOXICITY TESTING OF VOC MIXTURES IN HUMANS

In order to characterize the neurobehavioral effects of VOC exposure, a microprocessor-based test battery was used. The neurobehavioral evaluation system (NES) developed by Baker et al (1985) for neurotoxicity field testing contains a menu-driven battery of tests selected on the basis of proven sensitivity to environmental toxicity and WHO recommendations (Johnson et al., 1987). A variety of sensorimotor and cognitive functions including reaction time, motor coordination, attention, memory and spatial integration were assessed. The NES battery has been used previously in the study of nitrous dioxide (Greenberg et al, 1985), styrene, alcohol, is currently being used by CDC in the AGENT ORANGE project, and in NHANES III (National Health and Nutrition Survey). Specific tests to be used in the VOC study included finger tapping, continuous performance, digit span, symbol-digit substitution, visual memory and switching attention. Individual tests are described below.

NES TESTS USED IN VOC STUDY

(1)	Finger tapping (mean no.)	3 min.
(2)	Digit span (no. correct fwd, bwd)	7 min.
(3)	Continuous Performance Test (msec, errors)	7 min.
(4)	Symbol-digit substitution (sec/digit, errors)	5 min.
(5)	Serial digit learning (no. correct, no. trials)	7 min.
(6)	Pattern memory (no. correct, msec)	5 min.
(7)	Switching attention ((msec/no. correct)	7 min.
(8)	Mood scales (5 scale avs.)	5 min.

Total time: 46 min.

Descriptions of Individual Tests

(1) Finger-Tapping. This test evaluates motor response speed. The subject is instructed to press a button as many times as possible within a 1-second interval. In the first trial, the subject presses one button with the left hand, The second trial tests the right hand, and in the third trial, the subject alternately taps two buttons with the preferred hand. This test provided a straightforward measure of VOC effect on motor response. It was a negative control measure since VOCs were not expected to affect motor response per se.

(2) Digit Span. The auditory version of this widely used clinical test has been adapted from the Wechsler Adult Intelligence Scale (Wechsler, 1955). Subjects must enter into the computer progressively longer series of digits which are presented visually at a rate of one per sec by the computer. New digit sequences are created at each span length. After incorrectly responding to two trials at a span length, the task changes such that the digits must be entered in reverse order. This test has been used as a measure of short-term memory and attention in studies of solvent and lead toxicity (Hanninen, 1979). Molhave et al (1986) reported that digit span performance was impaired by exposure to the complex VOC mixture, a finding that the present study attempted to replicate.

(3) Continuous Performance Test (CPT). This test measures sustained visual attention by having the subject press a button upon seeing a large letter "S" when it is projected on a video display. Letters flash briefly (for about 50 msec) on the screen at a rate of one per second for five minutes. Recording and storage of individual response latencies permits the computation mean (and standard deviation) of reaction times. Omission and commission errors are also recorded. Molhave et al (1986) failed to observe any effect of VOC exposure on "graphic" CPT performance, but the present test is very

different and has proven to be sensitive to toxicant exposure in previous studies (Baker et al, 1988; Erstin et al, 1988; Mahoney et al, 1988).

(4) Symbol-Digit (SD) Substitution Test. This test is similar to the Digit-Symbol Substitution Test from the WAIS. SD evaluates speed and coding ability and has been found useful in previous studies of lead, carbon disulfide and solvent mixtures (Anger and Johnson, 1985). In this adaptation, nine symbols and digits are paired at the top of the screen and the subject has to press the digit keys corresponding to a re-ordered test set of the nine symbols. The time required to complete each SD set and the number of digits incorrectly matched are recorded. Five sets of nine SD pairs are presented in succession. The pairing of symbols with digits is varied between sets to avoid learning.

(5) Serial Digit Learning (SDL). This is a test of short-term memory and attention in which subjects are presented a series of 10 digits on the display screen at a rate of one per second. Upon completion they are asked to enter that series into the computer. The series is presented until two successive trials are performed correctly, or at most 8 times. The number of correct digits entered on each trial is recorded. The series is changed for each test session to avoid learning effects. This test is a variant of the digit-span test found to be sensitive to solvent and lead exposure (Anger and Johnson, 1985) and is similar to Supraspan in the neurotoxicity test battery developed by Eckerman et al (1985). Based on the digit span findings of Molhave et al (1986), we predicted that SDL performance would be impaired by VOC exposure.

(6) Pattern Memory (PM) Test. This test of short term visual memory involves the brief presentation of a block-like pattern followed by three similar figures, one of which is identical with the original pattern. The degree of correspondence of the two incorrect patterns to the correct one varies. The number of correct responses and the response time are recorded. While digit span and serial digit learning assessed verbal memory, PM examined if VOC exposure impaired visual memory.

(7) Switching Attention (SWAT). This test evaluated the effect of VOC exposure on selective attention with little memory demands. During two initial sets the subject is trained to respond differentially to target stimuli on the left or right side of the screen, and then to stimuli in the center of the screen pointing to the left or right. The target stimuli are large rectangles with inset arrows pointing left or right which may appear on the right or left side of the screen. In the third set of trials, these two response conditions are mixed. When the word on the screen is "SIDE", the subject must press the left button if the target stimulus is on the left and vice versa. When the word on the screen is "DIRECTION", then the subject must press the right button if the arrow points to the right and vice versa. The word on the screen is randomly assigned each trial. the numbers of incorrect responses and mean reaction-times are recorded. This test was chosen to clarify whether the Molhave et al digit span finding was due to memory or attentional impairment.

(8) Mood Scales. This test consists of a series of adjectives or phrases with which subjects rate themselves on their feelings. Similar instruments have been used to evaluate the efficacy of psychotherapeutic drugs and to classify individuals with various neurobehavioral disorders (McNair et al, 1971) The present test contains 25 items and yields a five-dimensional mood profile (tension, depression, anger, fatigue, confusion) by combining ratings on individual items. Prior studies have shown that this approach is sensitive in the evaluation of central nervous system effects of occupational lead exposure (Baker et al, 1984). Molhave et al (1986) reported that subjective ratings of sensory irritation (comfort) and air quality were altered by VOC exposure. The mood scale was chosen to clarify these findings by assessing which dimension(s) of mood were affected by VOC exposure.

(9) Associate Learning/Recall. This test is similar to the paired associate learning test in the Wechsler Memory Scale (Wechsler, 1945). Three letter names (e.g. Jan, Pat, Tom) are paired with occupations (e.g. florist, lawyer, plumber). Nine pairs were presented on the video monitor for two secs. each with one sec. intervals between pairs. After all pairs were presented, each name was displayed and subjects were required to select the appropriate

alternative from a list of occupations. Three trials were presented with the same pairings, but in different order. The score consisted of the total number of correct pairings in trials 1-3. A single recall trial with the same pairings was presented about 20 mins. later. This test provided an alternative type of memory challenge for testing VOC exposure effects.

(10) Pattern Comparison. This test is similar to the Pattern Memory Test described above and utilizes the same 10x10 character arrays. Three patterns are presented simultaneously on the video screen. Two patterns are identical and the third is slightly different. The task is to identify the odd array. 25 trials were presented. Two measures were recorded--the mean latency of correct trials 2-25 and the number of correct trials. Schmedtje et al (1988) found that performance on this test improved after administration of dextroamphetamine and worsened after scopalomine.

(11) Simple Reaction Time (SRT). SRT is the oldest tool in the psychologist's armamentarium. This visual task requires subjects to button-press as fast as possible when a large square is displayed on the screen. Nine blocks (five with the preferred hand and four with the nonpreferred hand) containing 12 trials each and variable intertrial intervals of 2-4 secs were used. Mean reaction times, excluding block one, were calculated for each hand. SRT tests have been used extensively in occupational field studies including workers exposed to solvents (Anger and Johnson, 1985).

(12) Grammatical Reasoning. This test was adapted from Baddeley (1968). Each trial consists of a logical sequence such as "A FOLLOWS B: AB" to which the subject must respond "true" or "false". Sequences vary along four dimensions: active-passive, positive-negative, true-false, and whether the first letter is A or B. Two blocks of 32 trials each were presented. Mean response time for all correct trials and the number of correct trials were recorded. This was the most difficult NES test used. Little evidence of the utility of this test in neurotoxicity testing is available.

(13) Horizontal Addition Test. Subjects were presented with 60 simple

addition problems in which three single digits were presented in a rov. Subjects were instructed to sum the digits as rapidly and accurately as possible. Responses had to be entered on the keyboard. Mean response times and number of correct trials were recorded. Subjects made very few errors. This test served primarily as a filler.

REFERENCES

Anger WK, Johnson BL. Chemicals affecting behavior. In: O'Donoghue JL (ed) Neurotoxicity of Industrial and Commercial Chemicals. CRC Press, Baton Rouge, 1985.

Baddeley, AD. A 3 minute reasoning test based on grammatical transformation. Psychonom Sci 1968, 10: 341-342.

Baker E, Letz R, Fidler A, etal. A computer-based neurobehavioral evaluation system for occupational and environmental epidemiology: Methodology and validation studies. Neurobehav Toxicol Teratol 1985, 7:369-377.

Baker E, Letz R, Eisen EA et al. Neurobehavioral effects of solvents in construction painters. J Occup Med, 1988, 30:116-123.

Eckerman D, Carroll J, Foree D, et al. An approach to brief field testing for neurotoxicity. ibid:387-393.

Estrin WJ, Moore P, Letz R, Wasch HH. The P300 event-related potential in potential in experimental nitrous oxide exposure. Clin Pharmacol Ther, 1988, 43:86-90.

Greenberg B, Moore P, Letz R, Baker E. Computerized assessment of human neurotoxicity: Senitivity to nitrous oxide exposure. Clin Pharmacol Therapeutics, 1985, 38:656-660.

Hanninen H. Psychological test methods: Sensitivity to long term chemical exposure at work. Neurobehav Toxicol Teratol, 1979, 1(supp 1):157-161.

Mahoney P, Moore PA, Baker EL, Letz R. Experimental nitrous oxide exposure as a model system for evaluating neurobehavioral tests. Toxicol., 1988, 49:449-457.

McNair DM, Lorr M, Drpopleman LF. EITS Manual--Profile of Mood States. San Diego: Educational and Testing Service, 1975.

Molhave L, Bach B, Pedersen OF. Human reactions to lov concentrations of volatile organic compounds. Environ Internat, 1986, 12:167-175.

Schmedtje, J.F., Oman C., Letz, R., Baker, E.L. Effects on scopalomine and dextroamphetamine on human performance. Aviat Space Environ Med, 1988, 59:407-410.

Wechsler D. A standardized memory scale for clinical use. J Psychol 1945, 19:87-95.

Wechsler D. Wechsler Adult Intelligence Scale Manual. Psychological Corporation, New York, 1955.

APPENDIX D

SYMPTOM QUESTIONNAIRE

SUBJECT ID:_____

DO YOU FEEL NOW THAT STAYING IN THE CHAMBER IS COMFORTABLE? (Y/N)

WOULD YOU BE SATISFIED WITH THIS AIR QUALITY IN YOUR OWN HOME? (Y/N)

WOULD YOU VENTILATE YOUR HOME MORE? (Y/N)

(1) DOES THE SKIN OF YOUR BODY FEEL IRRITATED OR ITCHY?
NOT AT ALL |----------|----------| VERY MUCH

(2) HOW IS THE NOISE LEVEL IN THE ROOM?
VERY QUIET |----------|----------| VERY NOISY

(3) DO YOUR EYES FEEL DRY OR WATERY?
VERY DRY |----------|----------| VERY WATERY

(4) DO YOU HAVE A HEADACHE RIGHT NOW?
NOT AT ALL |----------|----------| VERY STRONG

(5) DOES THE SKIN ON YOUR FACE FEEL WARM OR COLD?
VERY COLD |----------|----------| VERY WARM

(6) DO YOU FEEL SLUGGISH?
NOT AT ALL |----------|----------| VERY MUCH

(7) HOW IS THE ODOR LEVEL IN THE ROOM?
NO ODOR |----------|----------| VERY STRONG

(8) DO YOU FEEL ANY IRRITATION IN YOUR EYES?
NOT AT ALL |----------|----------| VERY STRONG

(9) DOES THE SKIN OF YOUR BODY FEEL WARM OR COLD?
VERY COLD |----------|----------| VERY WARM

(10) HOW IS THE LIGHT LEVEL IN THE ROOM?
VERY DARK |----------|----------| VERY BRIGHT

(11) HAVE YOU BEEN COUGHING?
NOT AT ALL |----------|----------| A LOT

(12) DOES YOUR FACE FEEL IRRITATED OR ITCHY?
NOT AT ALL |----------|----------| VERY MUCH

(13) HOW IS THE AIR HUMIDITY IN THE ROOM?
VERY DRY |----------|----------| VERY HUMID

(14) HOW IS THE MOVEMENT OF AIR IN THE ROOM?
VERY STILL |----------|----------| VERY DRAFTY

(15) DOES YOUR NOSE FEEL DRY OR IRRITATED?
NOT AT ALL |----------|----------| VERY MUCH

(16) HOW IS THE AIR TEMPERATURE IN THE ROOM?
VERY COLD |----------|----------| VERY HOT

(17) ARE YOU TIRED OR SLEEPY?
NOT AT ALL |----------|----------| VERY MUCH

(18) DOES THE SKIN OF YOUR BODY FEEL MOIST OR DRY?
NOT AT ALL |----------|----------| VERY MUCH

(19) DOES YOUR THROAT FEEL IRRITATED?
NOT AT ALL |----------|----------| VERY MUCH

(20) HOW IS THE QUALITY OF AIR IN THE ROOM?
VERY GOOD |----------|----------| VERY BAD

(21) DOES THE SKIN ON YOUR FACE FEEL DRY OR MOIST?
VERY DRY |----------|----------| VERY MOIST

(22) HOW HARD DID YOU HAVE TO CONCENTRATE ON THESE QUESTIONS?
VERY LITTLE |----------|----------| VERY MUCH

APPENDIX E

THE USE OF LINEAR POTENTIOMETERS FOR SUBJECTIVE ASSESSMENTS OF INDOOR AIR QUALITY

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Introduction

The principle of potentiometer assessment is called modified magnitude estimation and is based on a linear analog rating scale (Bond and Lader, 1974). Subjects may continuously indicate individual or collective ratings of any specified indoor climate factor presented in the form of questions with defined continuous answers between two well defined extremes.

Measuring Principles

Each subject has his own rating box (Fig. 1) with a sliding pointer that can be positioned along a 60 mm track. The device can be used in two modes. Ratings can be signalled by external prompt (e.g., a visual prompt on the subject's video screen or verbal instruction from the investigator) or ratings can be initated spontaneously by the subject whenever a change in indoor air quality is perceived. In this study comfort ratings were signalled every 15-30 minutes by video prompts or verbal instruction. The extremes were defined as "no irritation" and "unacceptably strong irritation". Prior to commencement of testing, the potentiometer pointer was positioned at the "no irritation" extreme.

Instructions to the Subject should include:

a) Definition of the endpoints and rating scale.

b) The nature of the indoor climate factor (s) to be rated.

c) That the measurement scale must be established by the subject himself.

d) That only the pointer should move and that nobody else should see the setting of the pointer.

e) That the scale includes a neutral range (e.g., at the "no irritation" end).

f) That the initial position of the pointer has no particular relationship to the present IAQ.

g) Operation of the box and pointer must be demonstrated and explained to subjects prior to its use.

h) The time intervals at which ratings are to be made should be specified.

i) If external timing is used, the subjects should be instructed to go to the box and make a simulated rating even if they don't feel any change. They may delay their rating if they are occupied with other tests when the sound signal appears.

j) The pointer must be set in a neutral position (i.e., no irritation) at the start of the tests.

k) Subjects should not move the pointer back to neutral and then to a new position when a rating is required. That is, if a change in rating is desired, the pointer should be moved from its previous position directly to the new position.

The Equipment

The rating box is shown in Figure 1. The box contained a linear potentiometer with sliding pointer which could be positioned along a one-dimensional 60 mm axis. A 5 volt power source in the breakout box supplied the voltage across the resistive arm to give a 0 to 5 volt output range. Due to a non-linear response in the 4 to 5 volt range, the slide was limited to a maximum output of 4 volts. Thus 0 volts corresponded to "no irritation" and 4 volts corresponded to "unacceptabley strong irritation". Each of the four potentiometer outputs was directed to an input channel of an analog-to-digital

realtime module mounted in the backplane of the Compaq Plus microcomputer control station. A BASIC algorithm automatically sampled each of the four channels simultanelusly every 15 minutes throughout the test day. Sampling was initiated manually two minutes after testing commenced to permit subjects to complete the initial comfort rating. Subjects were prompted on video monitors while testing and by operators over loudspeakers during break periods to set their comfort level prior to the 15 minute auto sampling. The algorithm converted the sampled digital units back to voltage units to store and report irritation in a range of 0.0 to 4.0.

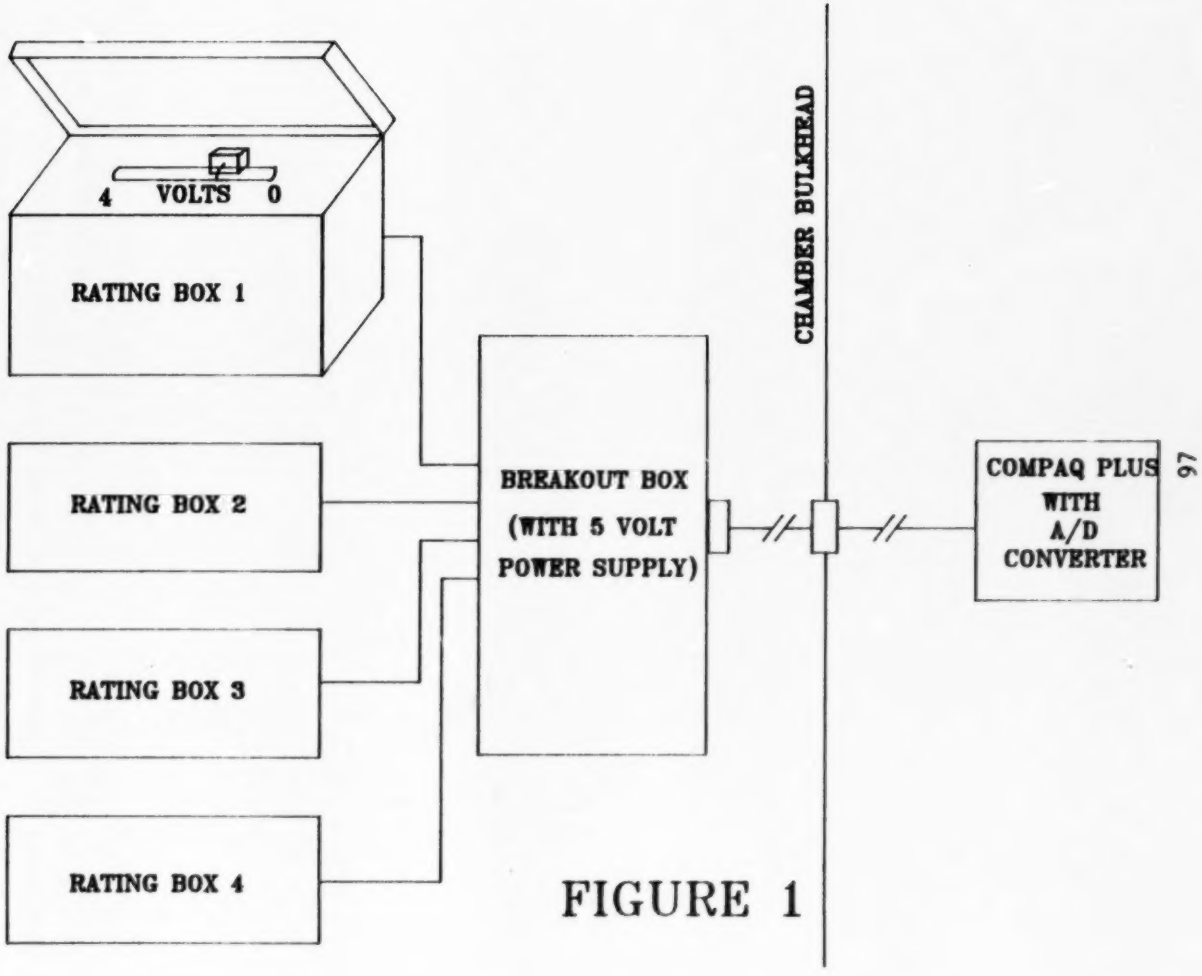
4 VOLTS 0
RATING BOX 1
RATING BOX 2
RATING BOX 3
RATING BOX 4
BREAKOUT BOX
(WITH 5 VOLT
POWER SUPPLY)
CHAMBER BULKHEAD
COMPAQ PLUS
WITH
A/D
CONVERTER
97

FIGURE 1

1

The calibration of the potentiometers with the analog-to-digital converter was checked prior to each test day and stored by the computer in 0, 25%, 50%, 75%, 100% increments of the slide of the potentiometer which corresponded to measures of 0.0, 1.0, 2.0, 3.0, and 4.0.

Instructions to the Subjects

"An aluminum Comfort Meter is located to the right of your computer. The lid should be open to show a sliding brass knob with a pointer that can be moved from "No irritation" to "Strong irritation". You will use this comfort meter to rate the degree of comfort or irritation that you feel in your eyes, nose or throat during the experiment. There are no scale markings on the box, so you will have to establish your own scale when you start".

"Remember, we want to monitor the level of comfort or irritation that you feel in your eyes, nose and throat during the experiment. You will be instructed at regular intervals, both by computer prompts and over the intercom, to indicate your comfort level. Do not interrupt an ongoing test to reset the comfort meter unless instructed to do so. During rest periods between tests, however, you are encouraged to indicate any change in comfort level that you feel. Please close the lid after each rating in order to prevent others from seeing your comfort rating".

REFERENCE

Bond A., and Lader M. The use of analoque scales in rating subjective feelings. Br. J. Med. Psycholo. 1974, 47:211-218.